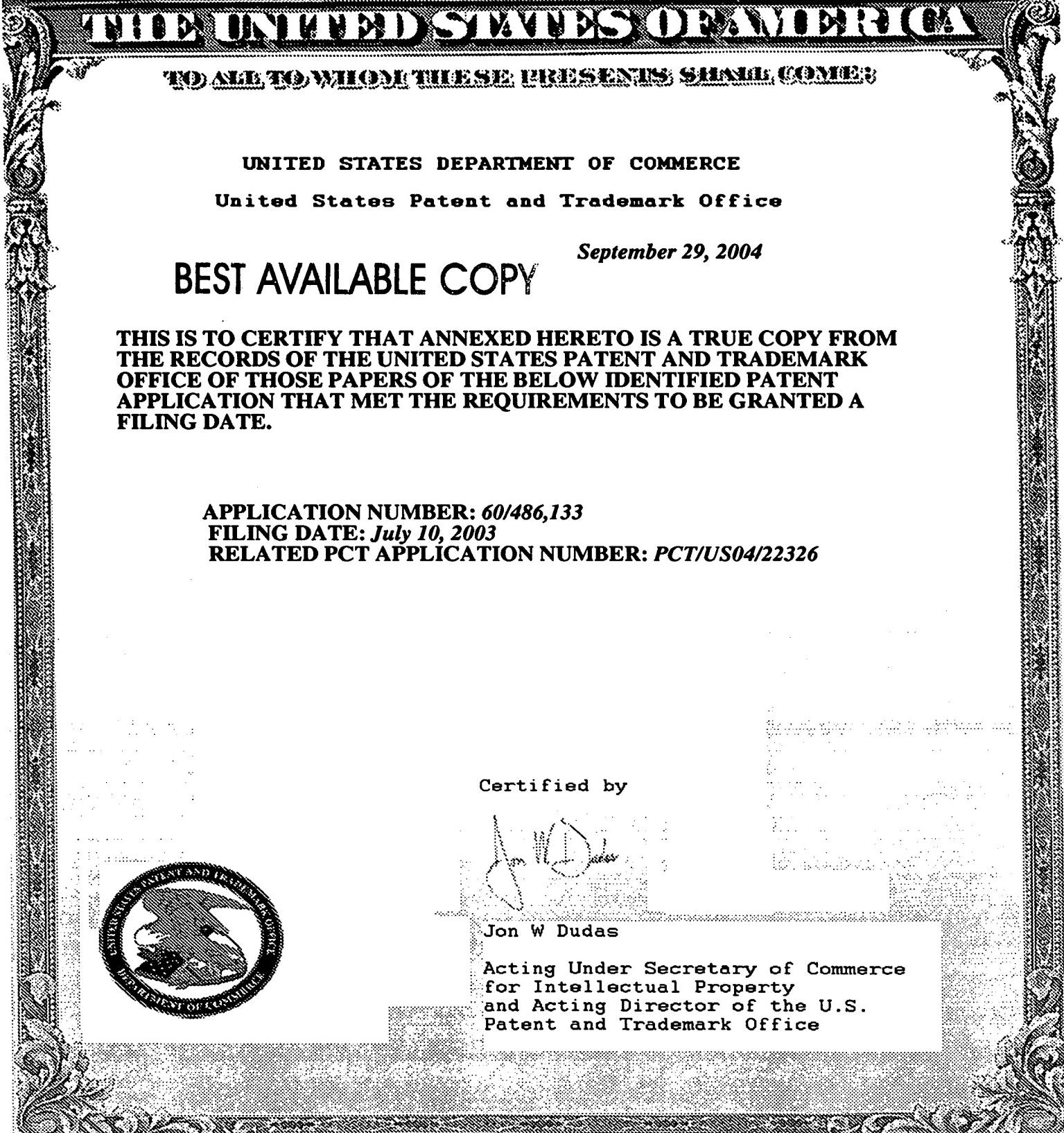


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**PROVISIONAL APPLICATION FOR UNITED STATES LETTERS PATENT IN THE UNITED
STATES PATENT AND TRADEMARK OFFICE**

5 Title: SUBSTITUTED HETEROCYCLIC DIARYLAMINE ANALOGUES

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SUBSTITUTED HETEROCYCLIC DIARYLAMINE ANALOGUES

FIELD OF THE INVENTION

5 This invention relates generally to substituted heterocyclic diarylamine analogues that are modulators of capsaicin receptors, and to the use of such compounds for treating conditions related to capsaicin receptor activation. The invention further relates to the use such compounds as probes for detecting and localizing capsaicin receptors.

10 BACKGROUND OF THE INVENTION

Pain perception, or nociception, is mediated by the peripheral terminals of a group of specialized sensory neurons, termed "nociceptors." A wide variety of physical and chemical stimuli induce activation of such neurons in mammals, leading to recognition of a potentially harmful stimulus. Inappropriate or excessive activation of nociceptors, however, can result in
15 debilitating acute or chronic pain.

Neuropathic pain involves pain signal transmission in the absence of stimulus, and typically results from damage to the nervous system. In most instances, such pain is thought to occur because of sensitization in the peripheral and central nervous systems following initial damage to the peripheral system (e.g., via direct injury or systemic disease). Neuropathic pain is
20 typically burning, shooting and unrelenting in its intensity and can sometimes be more debilitating than the initial injury or disease process that induced it.

Existing treatments for neuropathic pain are largely ineffective. Opiates, such as morphine, are potent analgesics, but their usefulness is limited because of adverse side effects, such as physical addictiveness and withdrawal properties, as well as respiratory depression,
25 mood changes, and decreased intestinal motility with concomitant constipation, nausea, vomiting, and alterations in the endocrine and autonomic nervous systems. In addition, neuropathic pain is frequently non-responsive or only partially responsive to conventional opioid analgesic regimens. Treatments employing the N-methyl-D-aspartate antagonist ketamine or the alpha(2)-adrenergic agonist clonidine can reduce acute or chronic pain, and permit a reduction in
30 opioid consumption, but these agents are often poorly tolerated due to side effects.

Topical treatment with capsaicin has been used to treat chronic and acute pain, including neuropathic pain. Capsaicin is a pungent substance derived from the plants of the Solanaceae family (which includes hot chili peppers) and appears to act selectively on the small diameter afferent nerve fibers (A-delta and C fibers) that are believed to mediate pain. The response to 5 capsaicin is characterized by persistent activation of nociceptors in peripheral tissues, followed by eventual desensitization of peripheral nociceptors to one or more stimuli. From studies in animals, capsaicin appears to trigger C fiber membrane depolarization by opening cation selective channels for calcium and sodium.

Similar responses are also evoked by structural analogues of capsaicin that share a 10 common vanilloid moiety. One such analogue is resiniferatoxin (RTX), a natural product of *Euphorbia* plants. The term vanilloid receptor (VR) was coined to describe the neuronal membrane recognition site for capsaicin and such related irritant compounds. The capsaicin response is competitively inhibited (and thereby antagonized) by another capsaicin analog, capsazepine, and is also inhibited by the non-selective cation channel blocker ruthenium red. 15 These antagonists bind to VR with no more than moderate affinity (typically with K_i values of no lower than 140 μM).

Rat and human vanilloid receptors have been cloned from dorsal root ganglion cells. The first type of vanilloid receptor to be identified is known as vanilloid receptor type 1 (VR1), and the terms "VR1" and "capsaicin receptor" are used interchangeably herein to refer to rat and/or 20 human receptors of this type, as well as mammalian homologs. The role of VR1 in pain sensation has been confirmed using mice lacking this receptor, which exhibit no vanilloid-evoked pain behavior, and impaired responses to heat and inflammation. VR1 is a nonselective cation channel with a threshold for opening that is lowered in response to elevated temperatures, low pH, and capsaicin receptor agonists. For example, the channel usually opens at temperatures 25 higher than about 45°C. Opening of the capsaicin receptor channel is generally followed by the release of inflammatory peptides from neurons expressing the receptor and other nearby neurons, increasing the pain response. After initial activation by capsaicin, the capsaicin receptor undergoes a rapid desensitization via phosphorylation by cAMP-dependent protein kinase.

Because of their ability to thus desensitize nociceptors in peripheral tissues, VR1 agonist 30 vanilloid compounds have been used as topical anesthetics. However, agonist application may itself cause burning pain, which limits this therapeutic use.

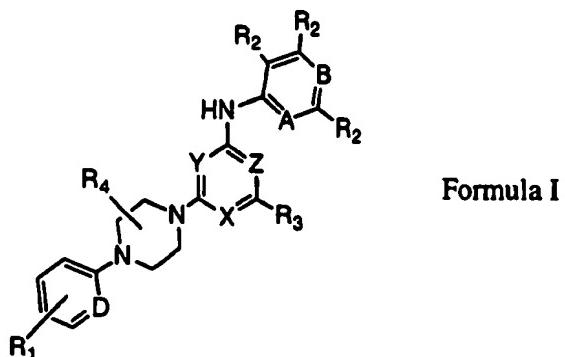
Thus, compounds that interact with VR1 but do not elicit the initial painful sensation of VR1 agonist vanilloid compounds, are desirable for the treatment of chronic and acute pain, including neuropathic pain. Antagonists of this receptor are particularly desirable for the treatment of pain, as well as conditions such as tear gas exposure, itch and urinary incontinence.

- 5 The present invention fulfills this need, and provides further related advantages.

SUMMARY OF THE INVENTION

The present invention provides compounds that modulate, preferably inhibit, VR1 activation. Within certain aspects, compounds provided herein are substituted heterocyclic

- 10 diarylamine analogues of Formula I:



Formula I

or a pharmaceutically acceptable form thereof. Within Formula I:

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

- 15 R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

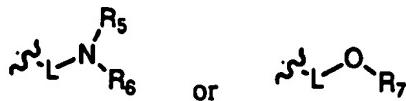
- 20 Each R₂ is:

(i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or

(ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl;

R₃ is selected from:

- 5 (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
(ii) C₁-C₆alkyl, phenyl and pyridyl; and
(iii) groups of the formula



wherein

- 10 L is a bond or C₁-C₆alkyl;

R₅ and R₆ are:

- (a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

- 15 (b) joined to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 methyl substituents.

Within certain aspects, compounds as described herein exhibit a K_i of no greater than 1 micromolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in a capsaicin receptor binding assay and/or have an IC₅₀ value of no greater than 1 micromolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in an assay for determination of capsaicin receptor

antagonist activity. Preferred compounds are generally those with higher potency (*i.e.*, lower K_i or lower IC_{50}).

In certain embodiments, compounds as described herein exhibit no detectable agonist activity in an *in vitro* assay of capsaicin receptor activation.

5 Within certain aspects, compounds and pharmaceutically acceptable forms thereof as described herein are labeled with a detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

10 The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one compound or pharmaceutically acceptable form thereof as described herein in combination with a physiologically acceptable carrier or excipient.

15 Within further aspects, methods are provided for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell (*e.g.*, neuronal) expressing a capsaicin receptor with an effective amount of at least one compound or pharmaceutically acceptable form thereof as described herein. Such contact may occur *in vivo* or *in vitro*.

20 Methods are further provided for inhibiting binding of vanilloid ligand to a capsaicin receptor. Within certain such aspects, the inhibition takes place *in vitro*. Such methods comprise contacting a capsaicin receptor with at least one compound or pharmaceutically acceptable form thereof as described herein, under conditions and in an amount sufficient to detectably inhibit vanilloid ligand binding to the capsaicin receptor. Within other such aspects, the capsaicin receptor is in a patient. Such methods comprise contacting cells expressing a capsaicin receptor in a patient with at least one compound or pharmaceutically acceptable form thereof as described herein in an amount sufficient to detectably inhibit vanilloid ligand binding to cells expressing a cloned capsaicin receptor *in vitro*, and thereby inhibiting binding of vanilloid ligand to the capsaicin receptor in the patient.

25 The present invention further provides methods for treating a condition responsive to capsaicin receptor modulation in a patient, comprising administering to the patient a capsaicin receptor modulatory effective amount of at least one compound or pharmaceutically acceptable form thereof as described herein.

30 Within other aspects, methods are provided for treating pain in a patient, comprising administering to a patient suffering from pain a capsaicin receptor modulatory amount of at least one compound or pharmaceutically acceptable form thereof as described herein.

Methods are further provided for treating itch, urinary incontinence, cough and/or hiccup in a patient, comprising administering to a patient suffering from one or more of the foregoing conditions a capsaicin receptor modulatory amount of at least one compound or pharmaceutically acceptable form thereof as described herein.

5 The present invention further provides methods for promoting weight loss in an obese patient, comprising administering to an obese patient a capsaicin receptor modulatory amount of at least one compound or pharmaceutically acceptable form thereof as described herein.

Within further aspects, the present invention provides methods for determining the presence or absence of capsaicin receptor in a sample, comprising: (a) contacting a sample with
10 a compound as described herein under conditions that permit binding of the compound to capsaicin receptor; and (b) detecting a level of the compound bound to capsaicin receptor.

The present invention also provides packaged pharmaceutical preparations, comprising:
(a) a pharmaceutical composition as described herein in a container; and (b) instructions for
15 using the composition to treat one or more conditions responsive to capsaicin receptor modulation, such as pain, itch, urinary incontinence, cough, hiccup, and/or obesity.

In yet another aspect, the invention provides methods of preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

20 DETAILED DESCRIPTION

As noted above, the present invention provides substituted heterocyclic diarylamine analogues. Such modulators may be used *in vitro* or *in vivo*, to modulate (preferably inhibit) capsaicin receptor activity in a variety of contexts.

25 TERMINOLOGY

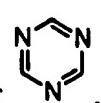
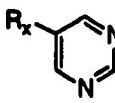
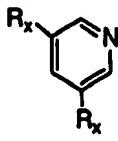
Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds
30 being included in the present invention unless otherwise specified. Where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but

rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (e.g., R₁-R₄, A, B, Z). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

The term "substituted heterocyclic diarylamine analogue," as used herein, encompasses all compounds of Formula I. In other words, compounds in which the core ring



is pyridyl, pyrimidyl or triazinyl (e.g.,



of which is optionally substituted as described herein) are specifically included within the definition of substituted heterocyclic diarylamine analogues.

"Pharmaceutically acceptable forms" of the compounds recited herein are pharmaceutically acceptable salts, hydrates, clathrates and prodrugs of such compounds. As used herein, a pharmaceutically acceptable salt is an acid or base salt that is generally considered in the art to be suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutical salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzene sulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alcanoic such as acetic, HOOC-(CH₂)_n-COOH where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein, including those listed by *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985).

A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a patient, to

produce a compound of Formula I. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulphydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulphydryl group, respectively. Examples of prodrugs 5 include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms (C_1 - C_8 alkyl), from 1 to 6 carbon atoms (C_1 - C_6 alkyl) and from 1 to 4 carbon atoms (C_1 - C_4 alkyl), such as methyl, ethyl, 10 propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. " C_0 - C_4 alkyl" refers to a bond or a C_1 - C_4 alkyl group; " C_0 - C_8 alkyl" refers to a bond or a C_1 - C_8 alkyl group.

Similarly, "alkenyl" refers to straight or branched chain alkene groups. Alkenyl groups include C_2 - C_8 alkenyl, C_2 - C_6 alkenyl and C_2 - C_4 alkenyl groups, which have from 2 to 8, 2 to 6 or 2 15 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C_2 - C_8 alkynyl, C_2 - C_6 alkynyl and C_2 - C_4 alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

A "cycloalkyl" is a saturated cyclic group in which all ring members are carbon, such as 20 cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. If substituted, any ring carbon atom may be bonded to any indicated substituent, such as halogen, cyano, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, or C_2 - C_8 alkanoyl.

By "alkoxy," as used herein, is meant an alkyl, alkenyl or alkynyl group as described above attached via an oxygen bridge. Alkoxy groups include C_1 - C_6 alkoxy and C_1 - C_4 alkoxy 25 groups, which have from 1 to 6 or 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexaoxy, 3-hexaoxy, and 3-methylpentoxy are specific alkoxy groups. Similarly, "alkyl thio" refers to an alkyl, alkenyl or alkynyl group as described above attached via a sulfur bridge.

"Alkylsulfonyl" refers to groups of the formula $-(SO_2)-alkyl$, in which the sulfur atom is the point of attachment. Alkylsulfonyl groups include C_1 - C_6 alkylsulfonyl and C_1 -

C_4 alkylsulfonyl groups, which have from 1 to 6 or 1 to 4 carbon atoms, respectively. Methylsulfonyl is one representative alkylsulfonyl group.

"Alkylsulfonamido" refers to groups of the formula $-(SO_2)-NR_2$, in which the sulfur atom is the point of attachment and each R is independently hydrogen or alkyl. The term "mono- or di- $(C_1-C_6$ alkyl)sulfonamido" refers to such groups in which one R is C_1-C_6 alkyl and the other R is hydrogen or an independently chosen C_1-C_6 alkyl.

The term "alkanoyl" refers to an acyl group in a linear, branched or cyclic arrangement (e.g., $-(C=O)$ -alkyl). Alkanoyl groups include C_2-C_8 alkanoyl, C_2-C_6 alkanoyl and C_2-C_4 alkanoyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively. " C_1 alkanoyl" refers to $-(C=O)-H$, which (along with C_2-C_8 alkanoyl) is encompassed by the term " C_1-C_8 alkanoyl." Ethanoyl is C_2 alkanoyl.

An "alkanone" is a ketone group in which carbon atoms are in a linear, branched or cyclic alkyl arrangement. " C_3-C_8 alkanone," " C_3-C_6 alkanone" and " C_3-C_4 alkanone" refer to an alkanone having from 3 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C_3 alkanone group has the structure $-CH_2-(C=O)-CH_3$.

Similarly, "alkyl ether" refers to a linear or branched ether substituent linked via a carbon-carbon bond. Alkyl ether groups include C_2-C_8 alkyl ether, C_2-C_6 alkyl ether and C_2-C_4 alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C_2 alkyl ether group has the structure $-CH_2-O-CH_3$.

"Alkylamino" refers to a secondary or tertiary amine having the general structure $-NH-$ alkyl or $-N(alkyl)(alkyl)$, wherein each alkyl may be the same or different. Such groups include, for example, mono- and di- $(C_1-C_8$ alkyl)amino groups, in which each alkyl may be the same or different and may contain from 1 to 8 carbon atoms, as well as mono- and di- $(C_1-C_6$ alkyl)amino groups and mono- and di- $(C_1-C_4$ alkyl)amino groups. Alkylaminoalkyl refers to an alkylamino group linked via an alkyl group (i.e., a group having the general structure $-alkyl-NH-alkyl$ or $-alkyl-N(alkyl)(alkyl)$). Such groups include, for example, mono- and di- $(C_1-C_8$ alkyl)amino C_1-C_8 alkyl, mono- and di- $(C_1-C_6$ alkyl)amino C_1-C_6 alkyl and mono- and di- $(C_1-C_4$ alkyl)amino C_1-C_4 alkyl, in which each alkyl may be the same or different.

The term "aminocarbonyl" refers to an amide group (i.e., $-(C=O)NH_2$). "Mono- or di- $(C_1-C_6$ alkyl)aminocarbonyl" refers to an amide group in which one or both of the hydrogen atoms is replaced with an independently chosen C_1-C_6 alkyl.

The term "halogen" includes fluorine, chlorine, bromine and iodine. A "haloalkyl" is a branched, straight-chain or cyclic alkyl group, substituted with 1 or more halogen atoms (e.g., "haloC₁-C₈alkyl" groups have from 1 to 8 carbon atoms; "haloC₁-C₆alkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; and mono-, di-, tri-, tetra- or penta-chloroethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl. Within certain compounds provided herein, not more than 5 or 3 haloalkyl groups are present. The term "haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "HaloC₁-C₈alkoxy" groups have 1 to 8 carbon atoms.

A dash ("") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

A "heteroatom," as used herein, is oxygen, sulfur or nitrogen.

A "heterocycloalkyl" is a saturated cyclic group in which at least one ring atom is a heteroatom. Heterocycloalkyl groups include, for example, morpholinyl, thiomorpholinyl, and tetrahydropyranyl.

A "carbocycle" or "carbocyclic group" comprises at least one ring formed entirely by carbon-carbon bonds (referred to herein as a carbocyclic ring), and does not contain a heterocyclic ring. Unless otherwise specified, each carbocyclic ring within a carbocycle may be saturated, partially saturated or aromatic. A carbocycle generally has from 1 to 3 fused, pendant or spiro rings, carbocycles within certain embodiments have one ring or two fused rings. Typically, each ring contains from 3 to 8 ring members (*i.e.*, C₃-C₈); C₅-C₇ rings are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain representative carbocycles are cycloalkyl (*i.e.*, groups that comprise saturated and/or partially saturated rings, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of any of the foregoing, such as cyclohexenyl), as well as aromatic groups (*i.e.*, groups that contain at least one aromatic carbocyclic ring, such as phenyl, benzyl, naphthyl, phenoxy, benzoxy, phenylethanonyl, fluorenyl, indanyl and 1,2,3,4-tetrahydro-naphthyl). Carbon atoms present within a carbocyclic ring may, of course, be further bonded to zero, one or two hydrogen atoms and/or any of a variety of ring substituents, such as hydroxy, halogen, cyano, nitro, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkyl ether,

C_3 - C_8 alkanone, C_1 - C_8 alkylthio, amino, mono- or di-(C_1 - C_8 alkyl)amino, C_3 - C_8 cycloalkyl C_0 - C_4 alkyl, halo C_1 - C_8 alkyl, halo C_1 - C_8 alkoxy, amino C_1 - C_8 alkyl, hydroxy C_1 - C_8 alkyl, C_1 - C_8 alkanoyl, C_1 - C_8 alkoxycarbonyl, -COOH, -C(=O)NH₂, mono- or di-(C_1 - C_8 alkyl)carboxamido, -S(O₂)NH₂, and/or mono- or di-(C_1 - C_8 alkyl)sulfonamido.

- 5 Certain carbocycles recited herein include C_6 - C_{10} aryl C_0 - C_6 alkyl groups (*i.e.*, groups in which a carbocyclic group comprising at least one aromatic ring is linked via a direct bond or a C_1 - C_6 alkyl group). Such groups include, for example, phenyl and indanyl, as well as groups in which either of the foregoing is linked via C_1 - C_6 alkyl, preferably via C_1 - C_4 alkyl. Phenyl groups linked via a direct bond or alkyl group may be designated phenyl C_0 - C_6 alkyl (*e.g.*, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl).

- 10 A "heterocycle" or "heterocyclic group" has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom, with the remaining ring atoms being carbon). Typically, a heterocyclic ring comprises 1-4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each 15 heterocyclic ring generally contains from 3 to 8 ring members (rings having from 5 to 7 ring members are recited in certain embodiments), and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Heterocycles may be optionally substituted at nitrogen and/or carbon atoms with a variety of substituents, such as those described above for carbocycles. Unless otherwise specified, a heterocycle may be a heterocycloalkyl 20 group (*i.e.*, each ring is saturated or partially saturated) or a heteroaryl group (*i.e.*, at least one ring within the group is aromatic). A heterocyclic group may generally be linked via any ring or substituent atom, provided that a stable compound results. N-linked heterocyclic groups are linked via a component nitrogen atom. A "heterocycle C_0 - C_8 alkyl" is a heterocyclic group linked via a direct bond or C_1 - C_8 alkyl group. A (3- to 10-membered heterocycle) C_1 - C_6 alkyl is a 25 heterocyclic group having from 3 to 10 ring members linked via a C_1 - C_6 alkyl group

- Heterocyclic groups include, for example, acridinyl, azepanyl, azocinyl, benzimidazolyl, benzimidazolinyl, benzisothiazolyl, benzisoxazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolylcarbazolyl, benztetrazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 30 dihydrofuro[2,3-b]tetrahydrofuran, dihydroisoquinolinyl, dihydrotetrahydrofuranyl, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, dithiazinyl, furanyl, furazanyl, imidazolinyl, imidazolidinyl, imidazolyl,

- indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isothiazolyl, isoxazolyl, isoquinolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl,
5 piperidinyl, piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridooxazolyl, pyridothiazolyl, pyridyl, pyrimidyl, pyrrolidinyl, pyrrolidonyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiadiazinyl, thiadiazolyl, thianthrenyl, thiazolyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thienyl, thiophenyl,
10 thiomorpholinyl and variants thereof in which the sulfur atom is oxidized, triazinyl, xanthenyl and any of the foregoing that are substituted with from 1 to 4 substituents as described above.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (*i.e.*, a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

20 Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Such optional substituents include, for example, hydroxy, halogen, cyano, nitro, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkyl ether, C₃-C₈alkanone, C₁-C₈alkylthio, amino, mono- or di-(C₁-C₈alkyl)amino, 25 haloC₁-C₈alkyl, haloC₁-C₈alkoxy, C₁-C₈alkanoyl, C₁-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, -COOH, -CONH₂, mono- or di-(C₁-C₈alkyl)carboxamido, -SO₂NH₂, and/or mono or di(C₁-C₈alkyl)sulfonamido, as well as carbocyclic and heterocyclic groups. Certain optionally substituted groups are substituted with from 0 to 3 independently selected substituents.

30 The terms "VR1," "type 1 vanilloid receptor" and "capsaicin receptor" are used interchangeably herein. Unless otherwise specified, these terms encompass both rat and human VR1 receptors (*e.g.*, GenBank Accession Numbers AF327067, AJ277028 and NM_018727;

sequences of certain human VR1 cDNAs are provided in SEQ ID NOs:1-3, and the encoded amino acid sequences shown in SEQ ID NOs:4 and 5, of U.S. Patent No. 6,482,611), as well as homologs thereof found in other species.

A "VR1 modulator," also referred to herein as a "modulator," is a compound that 5 modulates VR1 activation and/or VR1-mediated signal transduction. A VR1 modulator may be a VR1 agonist or antagonist although, for certain purposes described herein, a VR1 modulator preferably inhibits VR1 activation resulting from binding of a vanilloid ligand agonist (e.g., capsaicin or a capsaicin analogue such as olvanil or resiniferatoxin) to VR1. A modulator binds with "high affinity" if the K_i at VR1 is less than 1 micromolar, preferably less than 100 10 nanomolar, 10 nanomolar or 1 nanomolar. A representative assay for determining K_i at VR1 is provided in Example 5, herein. A modulator is considered an antagonist if it detectably inhibits vanilloid ligand binding to VR1 and/or VR1-mediated signal transduction (using, for example, the representative assay provided in Example 6); in general, such an antagonist inhibits VR1 activation with a IC_{50} value of less than 1 micromolar, preferably less than 100 nanomolar, and 15 more preferably less than 10 nanomolar or 1 nanomolar within the assay provided in Example 6. VR1 antagonists include neutral antagonists and inverse agonists. Compounds provided herein, as well as pharmaceutically acceptable forms thereof, are VR1 modulators.

An "inverse agonist" of VR1 is a compound that reduces the activity of VR1 below its basal activity level in the absence of added vanilloid ligand. Inverse agonists of VR1 may also 20 inhibit the activity of vanilloid ligand at VR1, and may also inhibit binding of vanilloid ligand to VR1. The ability of a compound to inhibit the binding of vanilloid ligand to VR1 may be measured by a binding assay, such as the binding assay given in Example 5. The basal activity of VR1, as well as the reduction in VR1 activity due to the presence of VR1 antagonist, may be determined from a calcium mobilization assay, such as the assay of Example 6.

A "neutral antagonist" of VR1 is a compound that inhibits the activity of vanilloid ligand 25 at VR1, but does not significantly change the basal activity of the receptor (*i.e.*, within a calcium mobilization assay as described in Example 6 performed in the absence of vanilloid ligand, VR1 activity is reduced by no more than 10%, more preferably by no more than 5%, and even more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). 30 Neutral antagonists of VR1 may inhibit the binding of vanilloid ligand to VR1.

As used herein an "agonist" of VR1 is a compound that elevates the activity of the receptor above the basal activity level of the receptor.

A "vanilloid ligand" is capsaicin or any capsaicin analogue that comprises a phenyl ring with two oxygen atoms bound to adjacent ring carbons, and that binds to VR1 with a K_i (determined as described herein) that is no greater than 10 μM . Vanilloid ligand agonists include capsaicin, olvanil, N-arachidonoyl-dopamine and resiniferatoxin (RTX). Vanilloid ligand antagonists include capsazepine and iodo-resiniferatoxin.

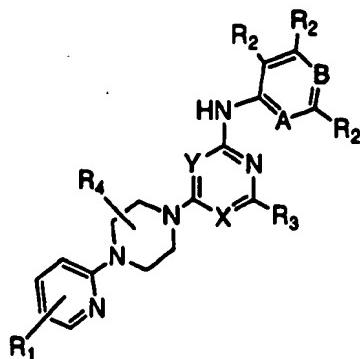
A "patient" is any individual treated with a VR1 modulator as provided herein. Patients include humans, as well as other animals such as companion animals (e.g., dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to capsaicin receptor modulation (e.g., pain, exposure to vanilloid ligand, itch, urinary incontinence, respiratory disorders, cough and/or hiccup), or may be free of such symptom(s) (i.e., treatment may be prophylactic).

VR1 MODULATORS

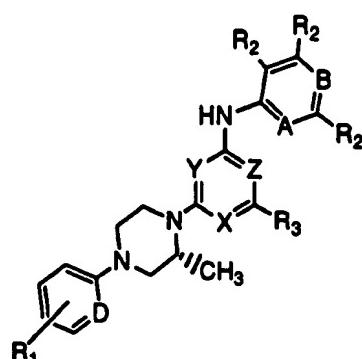
As noted above, the present invention provides VR1 modulators that may be used in a variety of contexts, including in the treatment of pain (e.g., neuropathic or peripheral nerve-mediated pain); exposure to capsaicin; exposure to acid, heat, light, tear gas air pollutants, pepper spray or related agents; respiratory conditions such as asthma or chronic obstructive pulmonary disease; itch; urinary incontinence; cough or hiccup; and/or obesity. VR1 modulators may also be used within *in vitro* assays (e.g., assays for receptor activity), as probes for detection and localization of VR1 and as standards in ligand binding and VR1-mediated signal transduction assays.

VR1 modulators provided herein are substituted heterocyclic diarylamine analogues that detectably modulate the binding of capsaicin to VR1 at nanomolar (i.e., submicromolar) concentrations, preferably at subnanomolar concentrations, more preferably at concentrations below 100 picomolar, 20 picomolar, 10 picomolar or 5 picomolar. Such modulators are preferably not capsaicin analogs (i.e., they do not comprise a phenyl ring with two oxygen atoms bound to adjacent ring carbons). Preferred modulators are VR1 antagonists and have no detectable agonist activity in the assay described in Example 6. In certain embodiments, such modulators further bind with high affinity to VR1, and do not substantially inhibit activity of human EGF receptor tyrosine kinase.

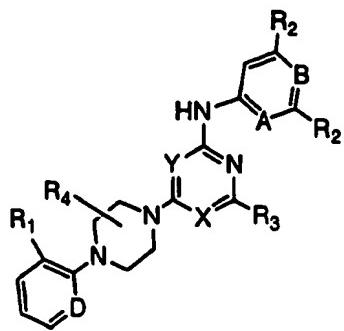
The present invention is based, in part, on the discovery that small molecules having the general Formula I, above, (as well as pharmaceutically acceptable forms thereof) are highly active modulators of VR1 activity. In certain embodiments, VR1 modulators provided herein further satisfy one or more of Formulas II – V, or are a pharmaceutically acceptable form 5 thereof, in which R₄, X, Y, Z, A, B and D are as described for Formula I and the remaining variables are as indicated below:



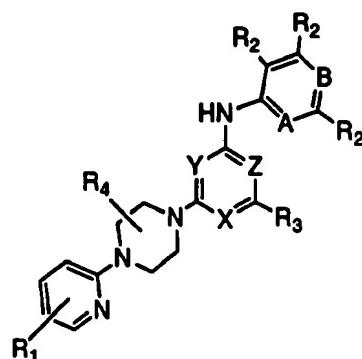
Formula II



Formula III



Formula IV



Formula V

Within Formula II:

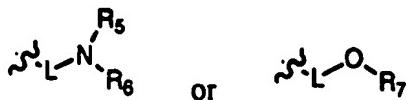
R₁ is as described for Formula I;

Each R₂ is:

- 10 (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or
- (ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl; and

R₃ is selected from:

- (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
- (ii) C₁-C₆alkyl, phenyl and pyridyl; and
- (iii) groups of the formula



wherein

L is a bond or C₁-C₆alkyl;

R₅ and R₆ are:

- (a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or
- (b) joined to form a 5- to 7-membered heterocycloalkyl; and

10 R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

15 wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl,

20 wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl.

Within Formula III, R₁, R₂ and R₃ are as described for Formula I.

Within Formula IV:

- 25 R₁ is halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- or di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)sulfonamido, or mono- or di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

- (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or
- 5 (ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl; and

R₃ is as described for Formula I.

Within Formula V:

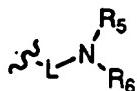
10 At least one of A and B is N; and

R₁, R₂ and R₃ are as described for Formula I.

In certain embodiments of Formulas I, II, III and V, at least one substituent represented by R₁ is located *ortho* to the point of attachment. In other words, if D is CH, an R₁ is located at the 2 position, and if D is N, an R₁ is located at the 3 position. For example, in certain 15 embodiments, R₁ represents a single substituent that is located at the *ortho* position. Such R₁ groups include, for example, fluoro, chloro, cyano, methyl, trifluoromethyl and methylsulfonyl.

Each R₂, within certain compounds of Formulas I, III and V is independently chosen from hydrogen, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido. For certain 20 compounds of Formula II and IV, R₂ is independently chosen from hydrogen, amino, cyano, halogen, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido. Preferably, at least one R₂ is not hydrogen, in certain embodiments, 1, 2 or 3 R₂ groups are not hydrogen.

R₃, in certain embodiments of Formulas I-V, is a group of the formula:



wherein

L is a bond or C₁-C₄alkyl; and

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₆alkyl and C₁-C₆alkenyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl;

each of which alkyl and heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, amino, hydroxy, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₄alkyl)amino.

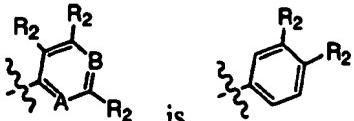
- 5 Such R₃ groups include, for example, mono- and di-(C₁-C₆alkyl)amino, pyrrolidinyl, morpholinyl, piperidinyl, and piperazinyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, amino, hydroxyl, C₁-C₄alkyl, cyano, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₆alkyl)amino.

In other embodiments, R₃ is $\sim^3 L-O-R_7$. Such R₃ groups include, for example,

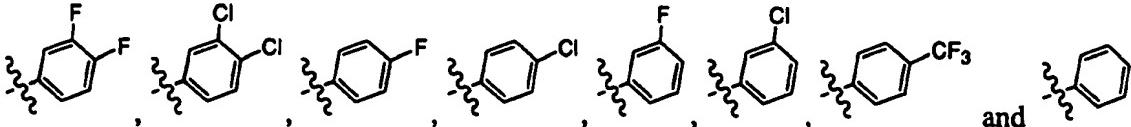
- 10 benzyloxy, optionally substituted with chlorine, fluorine or trifluoromethyl.

R₄, in certain compounds provided herein, represents one methyl group located at the 2-position of the piperazine group. The carbon to which such a methyl group is attached may, but need not, be chiral, with the R isomer generally preferred.

In certain embodiments of Formulas I-IV, A and B are CR₂. For example, the group:

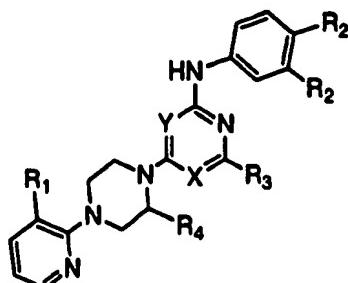


- 15 is within certain such compounds. Representative such groups include, for example:

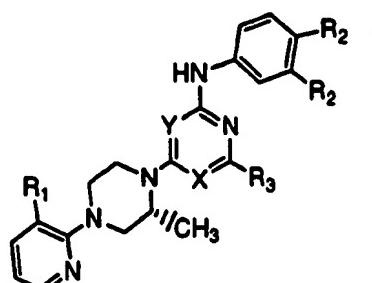


- In Formulas I, III and V, X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N. In certain embodiments, Z is N. For example, compounds 20 provided herein include those in which Z and X are N and Y is CR_x; Z and Y are N and X is CR_x; Z is N and X and Y are CR_x; or X, Y and Z are each N. In certain such embodiments, R_x is hydrogen. In other embodiments, X and Y are N and Z is CR_x. In Formulas II and IV, X and Y are independently CR_x or N. For example, such compounds include those in which X is CH and Y is N; Y is CH and X is N; or X and Y are both CH. R_x, in certain embodiments, is hydrogen, 25 methyl or cyano.

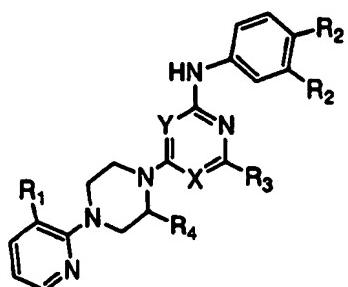
Within certain embodiments of Formulas II-V, compounds provided herein satisfy at least one of Formulas IIa – Va. Variables in each of these formulas are as described for Formulas II-V, respectively, except that R₄, when present, is hydrogen or methyl.



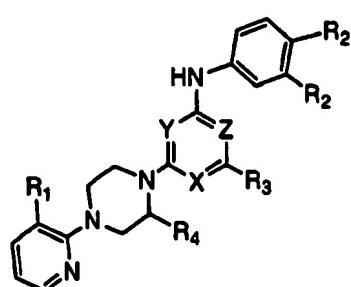
Formula IIa



Formula IIIa



Formula IVa



Formula Va

Within certain embodiments of Formulas IIa-Va, R₁ is fluoro, chloro, cyano, methyl or

- 5 trifluoromethyl; and R₃ is mono- or di-(C₁-C₆alkyl)amino, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl or benzyloxy, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxyl, C₁-C₄alkyl, cyano, C₁-C₄alkoxy and C₁-C₄haloalkyl. For such compounds of Formula IIa and IVa, each R₂ is independently chosen from hydrogen, halogen, cyano and C₁-C₄haloalkyl. For such compounds of Formula IIIa and Va,
- 10 each R₂ is independently chosen from hydrogen, halogen, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl.

Representative compounds provided herein include, but are not limited to, those specifically described in Examples 1-3. It will be apparent that the specific compounds recited therein are representative only, and are not intended to limit the scope of the present invention.

- 15 Further, as noted above, all compounds of the present invention may be present as a pharmaceutically acceptable form, such as a hydrate or acid addition salt.

Substituted heterocyclic diarylamine analogues provided herein detectably alter (modulate) vanilloid ligand-induced VR1 activity, as determined using a standard *in vitro* VR1 ligand binding assay and/or a functional assay such as a calcium mobilization assay, dorsal root

ganglion assay or *in vivo* pain relief assay. References herein to a "VR1 ligand binding assay" are intended to refer to a standard *in vitro* receptor binding assay such as that provided in Example 5, and a "calcium mobilization assay" (also referred to herein as a "signal transduction assay" is described in Example 6. Briefly, to assess VR1 binding, a competition assay may be

- 5 performed in which a VR1 preparation is incubated with labeled (e.g., ^{125}I) VR1 agonist and unlabeled test compound. Within the assays provided herein, the VR1 used is preferably a mammalian VR1, more preferably a human or rat VR1. The receptor may be recombinantly expressed or naturally expressed. The VR1 preparation may be, for example, a membrane preparation from HEK293 or CHO cells that recombinantly express human VR1 (such as a VR1
10 sequence provided in U.S. Patent No. 6,482,611). Incubation with a compound that detectably modulates vanilloid ligand binding to VR1 will result in a decrease or increase in the amount of label bound to the VR1 preparation, relative to the amount of label bound in the absence of the compound. This decrease or increase may be used to determine the K_i at VR1 as described herein. In general, compounds that decrease the amount of label bound to the VR1 preparation
15 within such an assay are preferred.

As noted above, compounds that are VR1 antagonists are preferred within certain embodiments. IC_{50} values for such compounds may be determined using a standard *in vitro* VR1-mediated calcium mobilization assay, as provided in Example 6. Briefly, cells expressing capsaicin receptor are contacted with a compound of interest and with an indicator of
20 intracellular calcium concentration (e.g., a membrane permeable calcium sensitivity dye such as Fluo-3 or Fura-2 (both of which are available, for example, from Molecular Probes, Eugene, OR), each of which produce a fluorescent signal when bound to Ca^{++}). Such contact is preferably carried out by one or more incubations of the cells in buffer or culture medium comprising either or both of the compound and the indicator in solution. Contact is maintained
25 for an amount of time sufficient to allow the dye to enter the cells (e.g., 1-2 hours). Cells are washed or filtered to remove excess dye and are then contacted with a vanilloid receptor agonist (e.g., capsaicin, RTX or olvanil), typically at a concentration equal to the IC_{50} concentration, and a fluorescence response is measured. When cells are contacted with a compound that is a VR1 antagonist, and with a vanilloid receptor agonist, the fluorescence response is generally reduced
30 by at least 20%, preferably at least 50% and more preferably at least 80%, as compared to cells that are contacted with the agonist in the absence of test compound. Alternatively, or in addition,

compounds may be evaluated for activity using a cultured dorsal root ganglion assay as provided in Example 9 and/or an *in vivo* pain relief assay as provided in Example 10. Compounds provided herein preferably have a statistically significant specific effect on VR1 activity within one or more such functional assays.

5 Within certain embodiments, modulators provided herein do not substantially modulate ligand binding to other cell surface receptors, such as EGF receptor tyrosine kinase or the nicotinic acetylcholine receptor. In other words, such modulators do not substantially inhibit activity of a cell surface receptor such as the human epidermal growth factor (EGF) receptor tyrosine kinase or the nicotinic acetylcholine receptor (*e.g.*, the IC₅₀ or IC₄₀ at such a receptor is
10 preferably greater than 1 micromolar, and most preferably greater than 10 micromolar). Preferably, a modulator does not detectably inhibit EGF receptor activity or nicotinic acetylcholine receptor activity at a concentration of 0.5 micromolar, 1 micromolar or more
15 preferably 10 micromolar. Assays for determining cell surface receptor activity are commercially available, and include the tyrosine kinase assay kits available from Panvera (Madison, WI).

Preferred compounds of the present invention are non-sedating. In other words, a dose of such compounds that is twice the minimum dose sufficient to provide analgesia in an animal model for determining pain relief (such as a model provided in Example 10, herein) causes only transient (*i.e.*, lasting for no more than ½ the time that pain relief lasts) or preferably no
20 statistically significant sedation in an animal model assay of sedation (using the method described by Fitzgerald et al. (1988) *Toxicology* 49(2-3):433-9). Preferably, a dose that is five times the minimum dose sufficient to provide analgesia does not produce statistically significant sedation. More preferably, a compound provided herein does not produce sedation at intravenous doses of less than 25 mg/kg (preferably less than 10 mg/kg) or at oral doses of less
25 than 140 mg/kg (preferably less than 50 mg/kg, more preferably less than 30 mg/kg).

If desired, compounds provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective concentrations of the compound to be achieved at oral doses of less than 140 mg/kg, preferably less than 50 mg/kg, more
30 preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a preferred compound is

nontoxic when a capsaicin receptor modulatory amount is administered to a subject), side effects (a preferred compound produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred compound exhibits an *in vitro* half-life that is equal to an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable for compounds used to treat pain by modulating CNS VR1 activity such that total daily oral doses as described above provide such modulation to a therapeutically effective extent, while low brain levels of compounds used to treat peripheral nerve mediated pain may be preferred (*i.e.*, such doses do not provide brain (*e.g.*, CSF) levels of the compound sufficient to significantly modulate VR1 activity). Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays. Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described within Example 7, herein.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, and (4) does not cause substantial release of liver enzymes.

As used herein, a compound that "does not substantially inhibit cellular ATP production" is a compound that satisfies the criteria set forth in Example 8, herein. In other words, cells treated as described in Example 8 with 100 µM of such a compound exhibit ATP levels that are

at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A compound that "does not significantly prolong heart QT intervals" is a compound that
5 does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of twice the minimum dose yielding a therapeutically effective *in vivo* concentration. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically
10 significant" is meant results varying from control at the p<0.1 level or more preferably at the p<0.05 level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

A compound "does not cause substantial liver enlargement" if daily treatment of laboratory rodents (e.g., mice or rats) for 5-10 days with twice the minimum dose that yields a
15 therapeutically effective *in vivo* concentration results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (e.g., dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more
20 than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a compound "does not promote substantial release of liver enzymes" if administration of twice the minimum dose yielding a therapeutically effective *in vivo* concentration does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more
25 than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels by more than 75% or 50% over matched controls. Alternately, a compound "does not promote substantial release of liver enzymes" if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) equivalent to two-fold the minimum *in vivo* therapeutic
30 concentration of the compound do not cause detectable release of any of such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In

more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the minimum *in vivo* therapeutic concentration of the compound.

- In other embodiments, certain preferred compounds do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the minimum therapeutically effective *in vivo* concentration.

- Certain preferred compounds are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay or the like) at a concentration equal to the minimum therapeutically effective *in vivo* concentration. In other embodiments, certain preferred compounds do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

- For detection purposes, as discussed in more detail below, compounds provided herein may be isotopically-labeled or radiolabeled. Accordingly, compounds recited in Formula I may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . In addition, substitution with heavy isotopes such as deuterium (*i.e.*, ^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PREPARATION OF VR1 MODULATORS

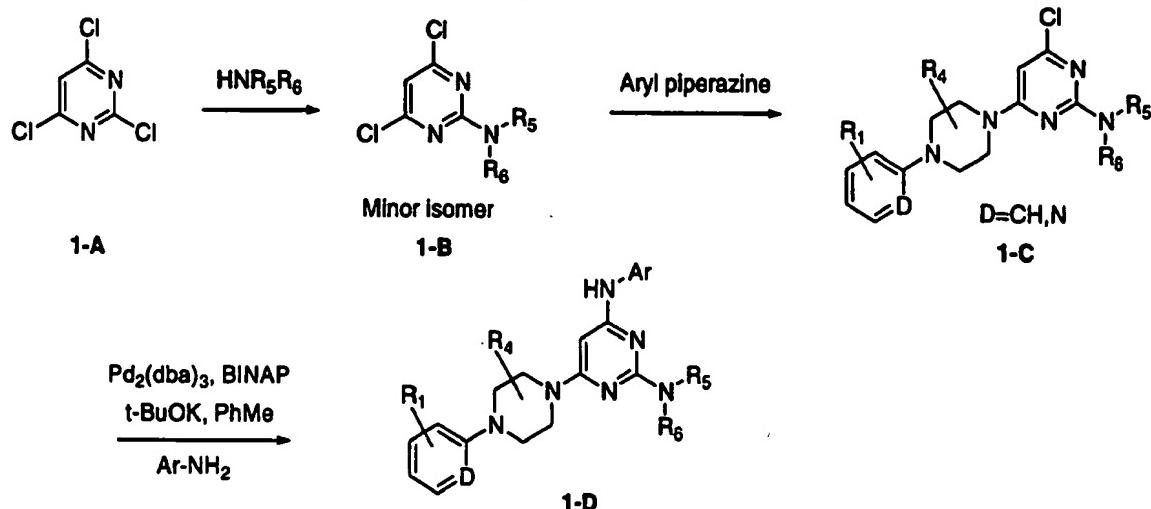
- Substituted heterocyclic diarylamine analogues may generally be prepared using standard synthetic methods. Starting materials are commercially available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of Schemes 1-4 may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Each variable in the following schemes refers to any group consistent with the description of the compounds provided herein.

In the schemes that follow, certain definitions are as follows:

Ar	an optionally substituted aromatic 6-membered ring
Aryl piperazine	piperazine substituted at the 4-position with an optionally substituted 6-membered aromatic ring, and optionally substituted with R ₄ at the 2, 3, 5 and/or 6 position of the piperazine
5	
BINAP	(<i>rac</i>)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Pd ₂ (dba) ₃	tris[dibenzylideneacetone]di-palladium
Ph	phenyl
t-BuOK	Potassium <i>tert</i> -butoxide

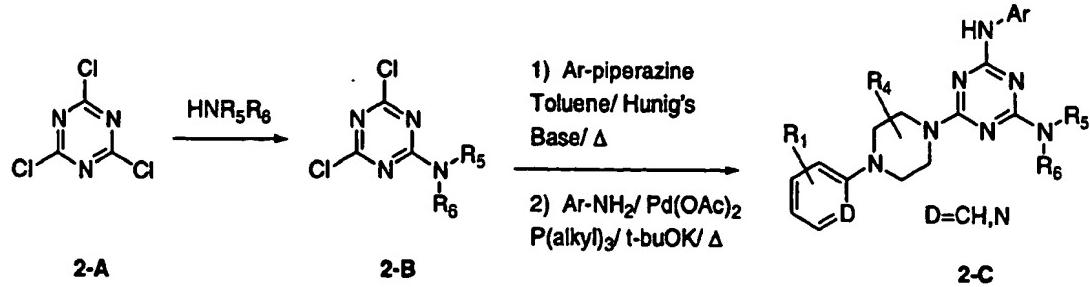
10

Scheme 1

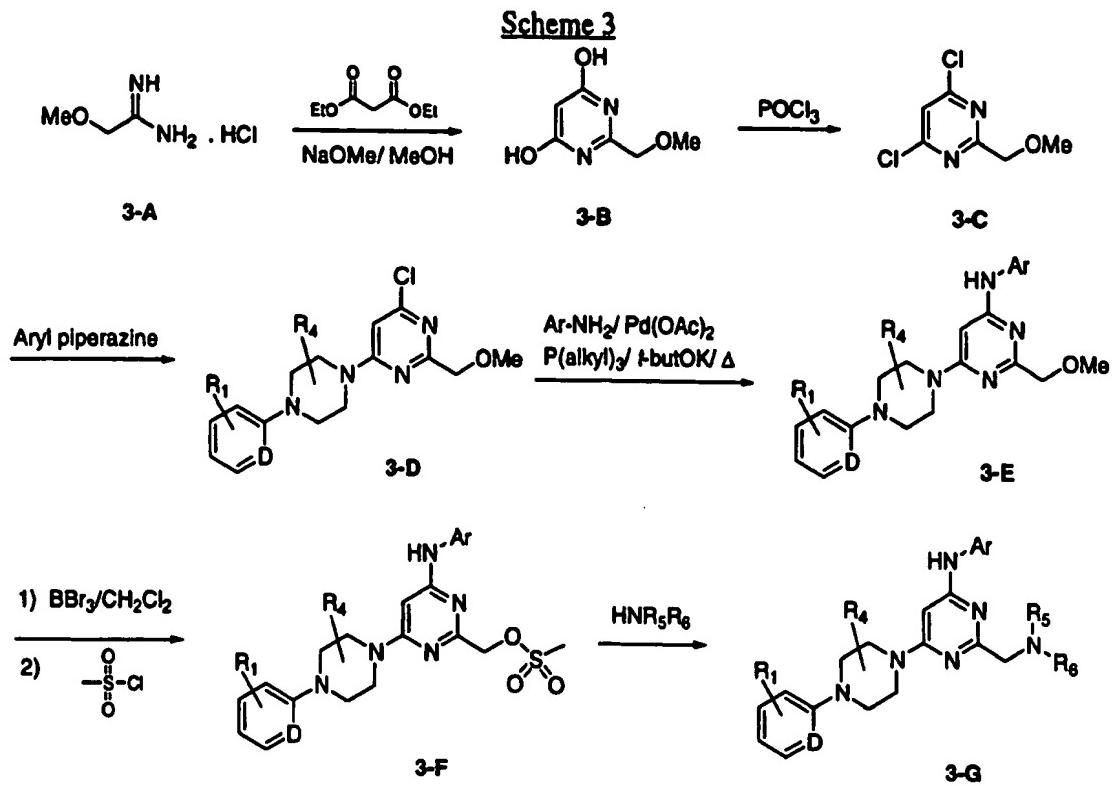


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Scheme 2

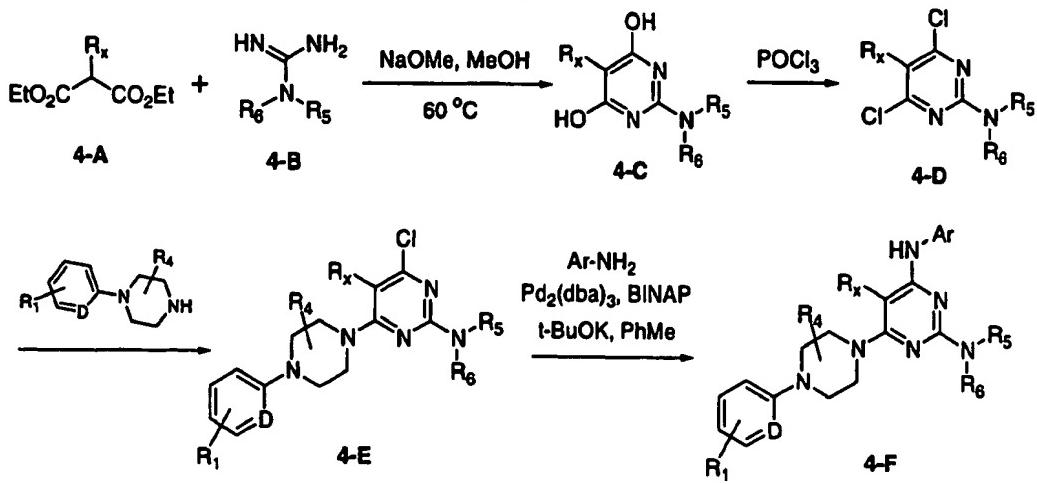


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5

Scheme 4



In certain embodiments, a VR1 modulator may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single

enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers include asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

5 As noted above, the present invention encompasses pharmaceutically acceptable forms of the compounds described herein. Such forms include pharmaceutically acceptable salts, hydrates, clathrates and prodrugs. A wide variety of synthetic procedures are available for the preparation of pharmaceutically acceptable salts. In general, a pharmaceutically acceptable salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional
10 chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

15 Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved to the parent compounds. Preferred prodrugs include acylated derivatives. Those of ordinary skill in the art will recognize various synthetic methods that may be employed to prepare prodrugs of the compounds provided herein.

20 Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (*e.g.*, ^{14}C), hydrogen (*e.g.*, ^3H), sulfur (*e.g.*, ^{35}S), or iodine (*e.g.*, ^{125}I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to
25 tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

30 The present invention also provides pharmaceutical compositions comprising one or more VR1 modulators, together with at least one physiologically acceptable carrier or excipient.

Pharmaceutical compositions may comprise, for example, one or more of water, buffers (e.g., neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents 5 such as EDTA or glutathione and/or preservatives. In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (e.g., 10 intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions suitable for oral use are preferred. Such compositions include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be 15 formulated as a lyophilizate. Formulation for topical administration may be preferred for certain conditions (e.g., in the treatment of skin conditions such as burns or itch).

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture 20 with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (e.g., calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (e.g., corn starch or alginic acid), binding agents (e.g., starch, gelatin or acacia) and lubricating agents (e.g., magnesium stearate, stearic acid or talc). The tablets may be uncoated or they may be 25 coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., calcium carbonate, calcium phosphate 30 or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (e.g., peanut oil, liquid paraffin or olive oil).

Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents (e.g., sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (e.g.,

5 naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from

10 fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil (e.g., arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

20 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

25 Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (e.g., olive oil or arachis oil), a mineral oil (e.g., liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (e.g., gum acacia or gum tragacanth), naturally-occurring phosphatides (e.g., soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (e.g., sorbitan monoleate) and

30 condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide

(e.g., polyoxyethylene sorbitan monoleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

Formulations for topical administration typically comprise a topical vehicle combined with active agent(s), with or without additional optional components. Suitable topical vehicles and additional components are well known in the art, and it will be apparent that the choice of a vehicle will depend on the particular physical form and mode of delivery. Topical vehicles include water; organic solvents such as alcohols (e.g., ethanol or isopropyl alcohol) or glycerin; glycals (e.g., butylene, isoprene or propylene glycol); aliphatic alcohols (e.g., lanolin); mixtures of water and organic solvents and mixtures of organic solvents such as alcohol and glycerin; lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile); and hydrocarbon-based materials such as microsponges and polymer matrices. A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling agents, preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained release materials. Examples of such components are described in Martindale--The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences. Formulations may comprise microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A topical formulation may be prepared in a variety of physical forms including, for example, solids, pastes, creams, foams, lotions, gels, powders, aqueous liquids and emulsions. The physical appearance and viscosity of such pharmaceutically acceptable forms can be governed by the presence and amount of emulsifier(s) and viscosity adjuster(s) present in the formulation. Solids are generally firm and non-pourable and commonly are formulated as bars or sticks, or in particulate form; solids can be opaque or transparent, and optionally can contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and

other active ingredients that increase or enhance the efficacy of the final product. Creams and lotions are often similar to one another, differing mainly in their viscosity; both lotions and creams may be opaque, translucent or clear and often contain emulsifiers, solvents, and viscosity adjusting agents, as well as moisturizers, emollients, fragrances, dyes/colorants, preservatives

- 5 and other active ingredients that increase or enhance the efficacy of the final product. Gels can be prepared with a range of viscosities, from thick or high viscosity to thin or low viscosity. These formulations, like those of lotions and creams, may also contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Liquids are thinner than creams,
- 10 lotions, or gels and often do not contain emulsifiers. Liquid topical products often contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product.

Suitable emulsifiers for use in topical formulations include, but are not limited to, ionic emulsifiers, cetearyl alcohol, non-ionic emulsifiers like polyoxyethylene oleyl ether, PEG-40 stearate, ceteareth-12, ceteareth-20, ceteareth-30, ceteareth alcohol, PEG-100 stearate and glyceryl stearate. Suitable viscosity adjusting agents include, but are not limited to, protective colloids or non-ionic gums such as hydroxyethylcellulose, xanthan gum, magnesium aluminum silicate, silica, microcrystalline wax, beeswax, paraffin, and cetyl palmitate. A gel composition may be formed by the addition of a gelling agent such as chitosan, methyl cellulose, ethyl cellulose, polyvinyl alcohol, polyquaterniums, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate. Suitable surfactants include, but are not limited to, nonionic, amphoteric, ionic and anionic surfactants. For example, one or more of dimethicone copolyol, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, lauramide DEA, cocamide DEA, and cocamide MEA, oleyl betaine, cocamidopropyl phosphatidyl PG-dimonium chloride, and ammonium laureth sulfate may be used within topical formulations. Suitable preservatives include, but are not limited to, antimicrobials such as methylparaben, propylparaben, sorbic acid, benzoic acid, and formaldehyde, as well as physical stabilizers and antioxidants such as vitamin E, sodium ascorbate/ascorbic acid and propyl gallate. Suitable moisturizers include, but are not limited to, lactic acid and other hydroxy acids and their salts, glycerin, propylene glycol, and butylene glycol. Suitable emollients include lanolin alcohol, lanolin, lanolin derivatives, cholesterol,

petrolatum, isostearyl neopentanoate and mineral oils. Suitable fragrances and colors include, but are not limited to, FD&C Red No. 40 and FD&C Yellow No. 5. Other suitable additional ingredients that may be included a topical formulation include, but are not limited to, abrasives, absorbents, anti-caking agents, anti-foaming agents, anti-static agents, astringents (*e.g.*, witch hazel, alcohol and herbal extracts such as chamomile extract), binders/excipients, buffering agents, chelating agents, film forming agents, conditioning agents, propellants, opacifying agents, pH adjusters and protectants.

An example of a suitable topical vehicle for formulation of a gel is: hydroxypropylcellulose (2.1%); 70/30 isopropyl alcohol/water (90.9%); propylene glycol (5.1%); and Polysorbate 80 (1.9%). An example of a suitable topical vehicle for formulation as a foam is: cetyl alcohol (1.1%); stearyl alcohol (0.5%); Quaternium 52 (1.0%); propylene glycol (2.0%); Ethanol 95 PGF3 (61.05%); deionized water (30.05%); P75 hydrocarbon propellant (4.30%). All percents are by weight.

Typical modes of delivery for topical compositions include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush; spraying (including mist, aerosol or foam spraying); dropper application; sprinkling; soaking; and rinsing. Controlled release vehicles can also be used.

A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The modulator, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting agents and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Modulators may also be formulated as suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt

in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Pharmaceutical compositions may be formulated as sustained release formulations (*i.e.*, a formulation such as a capsule that effects a slow release of modulator following administration).

- 5 Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of modulator release. The amount of modulator contained within a sustained release formulation depends
10 upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In addition to or together with the above modes of administration, a modulator may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking
15 water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Modulators are generally administered in a capsaicin receptor modulatory amount (*i.e.*, an amount that achieves a concentration in a body fluid (*e.g.*, blood, plasma, serum, CSF,
20 synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to inhibit the binding of vanilloid ligand to VR1 *in vitro*). A dose is considered to be therapeutically effective if it results in a discernible patient benefit, such as pain relief, as described herein. Preferred systemic doses are no higher than 50 mg per kilogram of body weight per day (*e.g.*, ranging from about 0.001 mg to about 50 mg per kilogram of body weight per day), with oral doses generally
25 being about 5-20 fold higher than intravenous doses (*e.g.*, ranging from 0.01 to 40 mg per kilogram of body weight per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage unit will vary depending, for example, upon the patient being treated and the particular mode of administration. Dosage units will generally contain between from
30 about 10 µg to about 500 mg of an active ingredient. Optimal dosages may be established using routine testing, and procedures that are well known in the art.

Pharmaceutical compositions may be packaged for treating conditions responsive to VR1 modulation (e.g., treatment of exposure to vanilloid ligand, pain, itch, obesity or urinary incontinence). Packaged pharmaceutical compositions may include a container holding a therapeutically effective amount of at least one VR1 modulator as described herein and

5 instructions (e.g., labeling) indicating that the contained composition is to be used for treating a condition responsive to VR1 modulation in the patient.

METHODS OF USE

VR1 modulators provided herein may be used as agonists or (preferably) antagonists of capsaicin receptors in a variety of contexts, both *in vitro* and *in vivo*. Within certain aspects,

10 VR1 antagonists may be used to inhibit the binding of vanilloid ligand agonist (such as capsaicin and/or RTX) to capsaicin receptor *in vitro* or *in vivo*. In general, such methods comprise the step of contacting a capsaicin receptor with a sufficient amount of one or more substituted heterocyclic diarylamine analogues, or pharmaceutically acceptable forms thereof, in the presence of vanilloid ligand in aqueous solution and under conditions otherwise suitable for

15 binding of the ligand to capsaicin receptor. The capsaicin receptor may be present in solution or suspension (e.g., in an isolated membrane or cell preparation), or in a cultured or isolated cell. Within certain embodiments, the capsaicin receptor is expressed by a neuronal cell present in a patient, and the aqueous solution is a body fluid. In general, the amount of Vr1 modulator(s) contacted with the receptor should yield a concentration in the aqueous solution sufficient to

20 inhibit vanilloid ligand binding to VR1 *in vitro* as measured, for example, using a binding assay as described in Example 5 and/or a calcium mobilization assay as described in Example 6. Preferably, one or more VR1 modulators are administered to an animal in an amount such that the analogue is present in at least one body fluid of the animal at a therapeutically effective concentration that is 100 nanomolar or less, preferably 50 nanomolar or less, 20 nanomolar or

25 less, or 10 nanomolar or less. For example, such compounds may be administered at a dose that is less than 20 mg/kg body weight, preferably less than 5 mg/kg and, in some instances, less than 1 mg/kg.

Also provided herein are methods for modulating, preferably inhibiting, the signal-transducing activity of a capsaicin receptor. Such modulation may be achieved by contacting a

30 capsaicin receptor (either *in vitro* or *in vivo*) with an effective amount of one or more VR1 modulators provided herein under conditions suitable for binding of the modulator(s) to the

receptor. The receptor may be present in solution or suspension, in a cultured or isolated cell preparation or within a patient. Modulation of signal transducing activity may be assessed by detecting an effect on calcium ion conductance (also referred to as calcium mobilization or flux). Modulation of signal transducing activity may alternatively be assessed by detecting an alteration 5 of a symptom (e.g., pain, burning sensation, broncho-constriction, inflammation, cough, hiccup, itch, and urinary incontinence) of a patient being treated with one or more VR1 modulators provided herein.

In general, an effective amount of VR1 modulator(s) is an amount sufficient to yield a concentration (in an aqueous solution that is in contact with the receptor) that is sufficient to 10 modulate VR1 signal transducing activity *in vitro* within a calcium mobilization assay as described in Example 6. VR1 modulator(s) provided herein are preferably administered to a patient (e.g., a human) orally or topically, and are present within at least one body fluid of the animal while modulating VR1 signal-transducing activity. Preferred VR1 modulators for use in such methods modulate VR1 signal-transducing activity *in vitro* at a concentration of 1 15 nanomolar or less, preferably 100 picomolar or less, more preferably 20 picomolar or less, and *in vivo* at a concentration of 100 nanomolar or less in a body fluid such as blood.

The present invention further provides methods for treating conditions responsive to VR1 modulation. Within the context of the present invention, the term "treatment" encompasses both disease-modifying treatment and symptomatic treatment, either of which may be prophylactic 20 (i.e., before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (i.e., after the onset of symptoms, in order to reduce the severity and/or duration of symptoms). A condition is "responsive to VR1 modulation" if it is characterized by inappropriate activity of a capsaicin receptor, regardless of the amount of vanilloid ligand present locally, and/or if modulation of capsaicin receptor activity results in alleviation of the condition 25 or a symptom thereof. Such conditions include, for example, symptoms resulting from exposure to VR1-activating stimuli, pain, respiratory disorders such as asthma and chronic obstructive pulmonary disease, itch, urinary incontinence, cough, hiccup, and obesity, as described in more detail below. Such conditions may be diagnosed and monitored using criteria that have been established in the art. Patients may include humans, domesticated companion animals and 30 livestock, with dosages as described above.

Treatment regimens may vary depending on the compound used and the particular condition to be treated. However, for treatment of most disorders, a frequency of administration of 4 times daily or less is preferred. In general, a dosage regimen of 2 times daily is more preferred, with once a day dosing particularly preferred. For the treatment of acute pain, a single dose that rapidly reaches effective concentrations is desirable. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy. In general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Patients experiencing symptoms resulting from exposure to capsaicin receptor-activating stimuli include individuals with burns caused by heat, light, tear gas or acid and those whose mucous membranes are exposed (e.g., via ingestion, inhalation or eye contact) to capsaicin (e.g., from hot peppers or in pepper spray) or a related irritant such as acid, tear gas or air pollutants. The resulting symptoms (which may be treated using compounds provided herein) may include, for example, pain, broncho-constriction and inflammation.

Pain that may be treated using the compounds provided herein may be chronic or acute and includes, but is not limited to, peripheral nerve-mediated pain (especially neuropathic pain). Compounds provided herein may be used in the treatment of, for example, postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache (dental pain), denture pain, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome and/or bilateral peripheral neuropathy. Additional neuropathic pain conditions include causalgia (reflex sympathetic dystrophy - RSD, secondary to injury of a peripheral nerve), neuritis (including, for example, sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis and Gombault's neuritis), neuronitis, neuralgias (e.g., those mentioned above, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial neuralgia, migranous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia,

mandibular joint neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia and vidian neuralgia), surgery-related pain, musculoskeletal pain, AIDS-related neuropathy, MS-related neuropathy, and spinal cord injury-related pain. Headache, including headaches involving peripheral nerve activity, such as sinus, cluster (*i.e.*, migrainous neuralgia) and some tension headaches and migraine, may also be treated as described herein. For example, migraine headaches may be prevented by administration of a compound provided herein as soon as a pre-migrainous aura is experienced by the patient. Further pain conditions that can be treated as described herein include "burning mouth syndrome," labor pains, Charcot's pains, intestinal gas pains, menstrual pain, acute and chronic back pain, hemorrhoidal pain, dyspeptic pains, angina, nerve root pain, homotopic pain and heterotopic pain – including cancer associated pain (*e.g.*, in patients with bone cancer), pain (and inflammation) associated with venom exposure (*e.g.*, due to snake bite, spider bite, or insect sting) and trauma associated pain (*e.g.*, post-surgical pain, pain from cuts, bruises and broken bones, and burn pain). Additional pain conditions that may be treated as described herein include pain associated with inflammatory bowel disease, irritable bowel syndrome and/or inflammatory bowel disease.

Within certain aspects, VR1 antagonists including (but not limited to) those specifically recited herein, may be used for the treatment of mechanical pain. As used herein, the term "mechanical pain" refers to pain other than headache pain that is not neuropathic or a result of exposure to heat, cold or external chemical stimuli. Mechanical pain includes physical trauma (other than thermal or chemical burns or other irritating and/or painful exposures to noxious chemicals) such as post-surgical pain and pain from cuts, bruises and broken bones; toothache, denture pain; nerve root pain; osteoarthritis; rheumatoid arthritis; fibromyalgia; meralgia paresthetica; back pain; cancer-associated pain; angina; carpal tunnel syndrome; and pain resulting from bone fracture, labor, hemorrhoids, intestinal gas, dyspepsia, and menstruation. Any VR1 antagonist that binds to VR1 with a Ki of less than 100 μ M and/or inhibits VR1 activity with an EC₅₀ of less than or equal to 100 μ M (determined as described herein) may be used. Preferably, the VR1 antagonist used is not a capsaicin analogue; particularly preferred VR1 antagonists are those provided herein.

Itching conditions that may be treated include psoriatic pruritis, itch due to hemodialysis, aguagenic pruritus, and itching associated with vulvar vestibulitis, contact dermatitis, insect bites

and skin allergies. Urinary incontinence, as used herein, includes detrusor hyperflexia of spinal origin and bladder hypersensitivity, both of which may be treated as described herein. Compounds provided herein may also be used as anti-tussive agents (to prevent, relieve or suppress coughing) and for the treatment of hiccup, and to promote weight loss in an obese patient. Therapeutically effective amounts for use in such methods are generally sufficient to provide detectable relief from the condition being treated.

Within other aspects, VR1 antagonists provided herein may be used within combination therapy for the treatment of conditions involving inflammatory components. Such conditions include, for example, autoimmune disorders and pathologic autoimmune responses known to have an inflammatory component including, but not limited to, arthritis (especially rheumatoid arthritis), psoriasis, Crohn's disease, lupus erythematosus, irritable bowel syndrome, tissue graft rejection, and hyperacute rejection of transplanted organs. Other such conditions include trauma (e.g., injury to the head or spinal cord), cardio- and cerebo-vascular disease and certain infectious diseases.

Within such combination therapy, a VR1 antagonist is administered to a patient along with an anti-inflammatory agent. The VR1 antagonist and anti-inflammatory agent may be present in the same pharmaceutical composition, or may be administered separately in either order. Anti-inflammatory agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), non-specific and cyclooxygenase-2 (COX-2) specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor (TNF) receptor antagonists, anti-TNF alpha antibodies, anti-C5 antibodies, and interleukin-1 (IL-1) receptor antagonists. Examples of NSAIDs include, but are not limited to ibuprofen (e.g., ADVIL™, MOTRIN™), flurbiprofen (ANSAID™), naproxen or naproxen sodium (e.g., NAPROSYN, ANAPROX, ALEVE™), diclofenac (e.g., CATAFLAM™, VOLTAREN™), combinations of diclofenac sodium and misoprostol (e.g., ARTHROTECT™), sulindac (CLINORIL™), oxaprozin (DAYPRO™), diflunisal (DOLOBID™), piroxicam (FELDENE™), indomethacin (INDOCIN™), etodolac (LODINE™), fenoprofen calcium (NALFON™), ketoprofen (e.g., ORUDIS™, ORUVAIL™), sodium nabumetone (RELAFENT™), sulfasalazine (AZULFIDINE™), tolmetin sodium (TOLECTIN™), and hydroxychloroquine (PLAQUENIL™). A particular class of NSAIDs consists of compounds that inhibit cyclooxygenase (COX) enzymes, such as celecoxib (CELEBREX™) and rofecoxib (VIOXX™).

NSAIDs further include salicylates such as acetylsalicylic acid or aspirin, sodium salicylate, choline and magnesium salicylates (TRILISATE™), and salsalate (DISALCID™), as well as corticosteroids such as cortisone (CORTONE™ acetate), dexamethasone (e.g., DECADRON™), methylprednisolone (MEDROL™) prednisolone (PRELONE™), prednisolone sodium phosphate (PEDIAPRED™), and prednisone (e.g., PREDNICEN-M™, DELTASONE™, STERAPRED™).

Suitable dosages for VR1 antagonist within such combination therapy are generally as described above. Dosages and methods of administration of anti-inflammatory agents can be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In certain embodiments, the combination administration of a VR1 antagonist with an anti-inflammatory agent results in a reduction of the dosage of the anti-inflammatory agent required to produce a therapeutic effect. Thus, preferably, the dosage of anti-inflammatory agent in a combination or combination treatment method of the invention is less than the maximum dose advised by the manufacturer for administration of the anti-inflammatory agent without combination administration of a VR1 antagonist. More preferably this dosage is less than $\frac{1}{4}$, even more preferably less than $\frac{1}{2}$, and highly preferably, less than $\frac{1}{4}$ of the maximum dose, while most preferably the dose is less than 10% of the maximum dose advised by the manufacturer for administration of the anti-inflammatory agent(s) when administered without combination administration of a VR1 antagonist. It will be apparent that the dosage amount of VR1 antagonist component of the combination needed to achieve the desired effect may similarly be affected by the dosage amount and potency of the anti-inflammatory agent component of the combination.

In certain preferred embodiments, the combination administration of a VR1 antagonist with an anti-inflammatory agent is accomplished by packaging one or more VR1 antagonists and one or more anti-inflammatory agents in the same package, either in separate containers within the package or in the same contained as a mixture of one or more VR1 antagonists and one or more anti-inflammatory agents. Preferred mixtures are formulated for oral administration (e.g., as pills, capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the one or more VR1 antagonists and one or more anti-inflammatory agents are to be taken together for the treatment of an inflammatory pain condition. A highly preferred combination is one in which the anti-inflammatory agent(s)

include at least one COX-2 specific cyclooxygenase enzyme inhibitor such as valdecoxib (BEXTRA®), lumiracoxib (PREXIGE™), etoricoxib (ARCOXIA®), celecoxib (CELEBREX®) and/or rofecoxib (VIOXX®).

The methods discussed above generally employ modulators that are VR1 antagonists; 5 however, methods are also provided herein that employ modulators that are VR1 agonists. Such modulators may be used, for example, in crowd control (as a substitute for tear gas) or personal protection (e.g., in a spray formulation) or as pharmaceutical agents for the treatment of pain, itch or urinary incontinence via capsaicin receptor desensitization. In general, compounds for use in crowd control or personal protection are formulated and used according to conventional 10 tear gas or pepper spray technology.

Within separate aspects, the present invention provides a variety of non-pharmaceutical *in vitro* and *in vivo* uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of capsaicin receptor (in samples such as cell preparations or tissue sections, preparations or fractions thereof). Compounds may 15 also be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to capsaicin receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize capsaicin receptors in living subjects. For example, a VR1 modulator may be labeled using any of a variety of well known techniques (e.g., 20 radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (e.g., determined by first assaying a time course of binding). Following incubation, unbound compound is removed (e.g., by washing), and bound compound detected using any method suitable for the label employed (e.g., autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect 25 luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (e.g., 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of capsaicin receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of capsaicin receptor in cultured cells or 30 tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

Modulators provided herein may also be used within a variety of well known cell separation methods. For example, modulators may be linked to the interior surface of a tissue culture plate or other support, for use as affinity ligands for immobilizing and thereby isolating, capsaicin receptors (e.g., isolating receptor-expressing cells) *in vitro*. Within one preferred embodiment, a modulator linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed (or isolated) by fluorescence activated cell sorting (FACS).

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification.

10

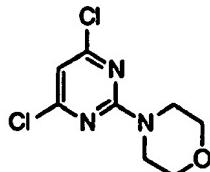
EXAMPLES

EXAMPLE 1

Preparation of 4-[4-(3-chloro-4-fluoro-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl]-morpholine

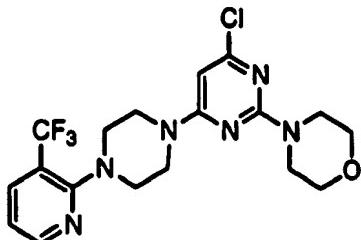
15 This Example illustrates the preparation of the representative substituted heterocyclic diarylamine analogue 4-[4-(3-chloro-4-fluoro-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl]-morpholine.

1. 6-morpholino-2,4-dichloropyrimidine



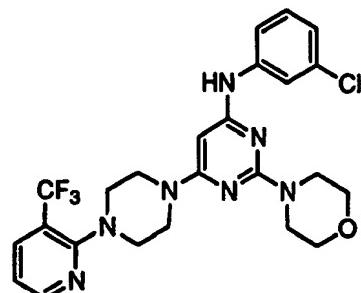
20 To an ice-cold solution containing 2,4,6-trichloropyrimidine (8 g, 44 mmol) in methanol (80 mL) and NaHCO₃ (10 g) add slowly and dropwise a methanolic solution (20 mL) of morpholine (4 mL, 46 mmol). Allow the mixture to warm to 25°C and stir overnight. Dilute with water, vigorously stir for 1 hour, and filter to give a white crystalline solid (10 g) as a mixture of regioisomers. Carefully recrystallize from toluene to give 4.5 g of 6-morpholino-2,4-dichloropyrimidine. Concentrate the mother liquor and carefully recrystallize from EtOH to give 3 g of 4,6-dichloro-2-morpholinopyrimidine.

2. 4-[4-Chloro-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl]-morpholine



To a rubber-septum-capped vial containing 4,6-dichloro-2-morpholinopyrimidine (0.2 M in dioxane, 0.25 mL) and 4-(6-trifluoromethyl-2-pyridyl)piperazine (0.2 M in dioxane, 0.28 mL) add aqueous K₃PO₄ (0.5 M, 0.125 mL). Heat the mixture at 90°C for 24 hours. Cool the mixture and concentrate under reduced pressure. Partition between ethyl acetate and water, dry (NaSO₄) the organic layer and concentrate under reduced pressure. Filter the crude product through a pad of silica gel (1:1 ethyl acetate/hexanes) and remove the solvent under reduced pressure to give the title compound.

3. (3-Chloro-phenyl)-{2-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine

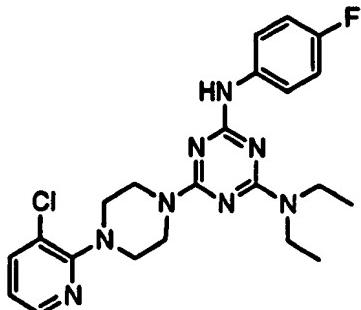


To a de-gassed mixture of 4-[4-Chloro-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl]-morpholine (134 mg, 0.258 mmol)), 3-chloroaniline (36 mg, 0.284 mmol), and 1M (THF) potassium *tert*-butoxide (0.516 mmol), in dioxane (4mL) under nitrogen, add Pd(OAc)₂ (0.01 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.013 mmol). Stir the mixture at 80°C for 16 hours, concentrate and extract with EtOAc. Dry over Na₂SO₄, concentrate under vacuum, and purify by preparative TLC (1:3 hexanes/EtOAc) to give (3-Chloro-phenyl)-{2-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine.

EXAMPLE 2
Preparation of Additional Representative Compounds

This Example illustrates the preparation of additional representative substituted heterocyclic diarylamine analogues.

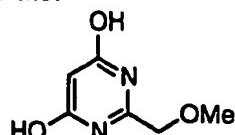
- 5 **A. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(4-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine**



To a rubber septum-capped vial containing (4,6-Dichloro-[1,3,5]triazin-2-yl)-diethyl-amine (0.2 M in toluene, 0.10 mL) and 4-(6-chloro-2-pyridyl)piperazine (0.2 M in toluene, 0.11 mL), add N,N-diisopropylethylamine (1 M in toluene, 0.05 mL). Heat the mixture at 60°C for 0.5 hours. After cooling, remove the volatiles by evaporation *in vacuo* (40°C at 2 torr) and add 4-fluoroaniline (0.2 M in toluene, 0.11 mL). Charge the reaction vessel with argon. Add 0.05 mL of 0.01M palladium solution prepared *in situ* as follows: Mix equal volumes of 0.02 M Pd(OAc)₂ in toluene and 0.05 M 2-(dicyclohexylphosphino)biphenyl in toluene. Add potassium 15 *tert*-butoxide (1M in THF, 0.05 mL) to the reaction mixture and heat at 80°C for 2 hours. Quench by adding 3N HCl (0.025 mL), dilute with ethyl acetate (0.5 mL), and load the whole mixture onto a 6-mL cartridge containing 1 g of SCX (a benzenesulfonic acid-impregnated silica gel strong cation exchanger). Wash the SCX cartridge with ethyl acetate (4 mL) and then elute the product with 10% Et₃N in EtOAc (5 mL). Concentrate the eluent to give the pure product:
20 LCMS (m/e); 456.

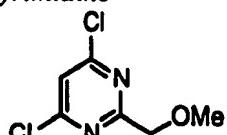
- B. (3,4-difluoro-phenyl)-{2-morpholin-4-ylmethyl}-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl-amine**

- 25 **1. 2-methoxymethyl-pyrimidine-4,6-diol**



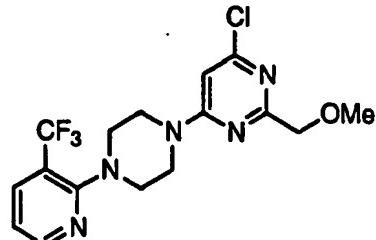
Reflux the mixture of malonic acid diethyl ester (7.96 g, 50 mmol), 2-methoxy-acetamidine hydrochloride (6.2 g, 50 mmol), and NaOMe methanol solution (4.37 M, 22.7 mL, 100 mmol) in MeOH (30 mL) for 24 hours. Concentrate, dilute with H₂O (50 mL), wash with EtOAc, and concentrate the aqueous layer. Extract with the solid with MeOH and concentrate to afford 2-methoxymethyl-pyrimidine-4,6-diol.

5 **2. 4,6-dichloro-2-methoxymethyl-pyrimidine**



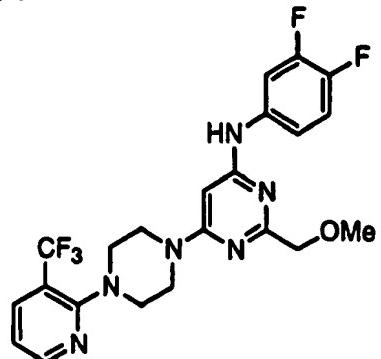
Reflux the mixture of 2-methoxymethyl-pyrimidine-4,6-diol (4.1 g) and POCl₃ (30 mL)
10 for 2 hours. Cool to room temperature, concentrate, partition between saturated aqueous NaHCO₃ and EtOAc. Dry over Na₂SO₄, concentrate under vacuum, and purify by flash column chromatography (2:1 hexanes/EtOAc) to give 4,6-dichloro-2-methoxymethyl-pyrimidine.

15 **3. 4-chloro-2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidine**



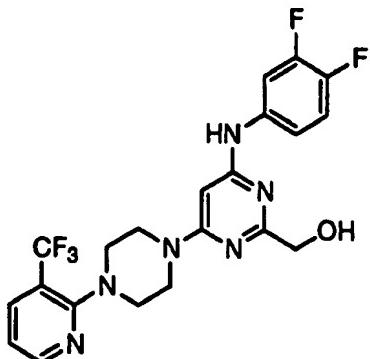
Combine 4,6-dichloro-2-methoxymethyl-pyrimidine (800 mg, 4.14 mmol), 1-(3-trifluoromethyl-pyridin-2-yl)-piperazine (960 mg, 4.14 mmol), sodium bicarbonate (500 mg), and ethanol (50 mL). Reflux for 4 hours, let cool to room temperature, vacuum filter, and evaporate the mother liquor. Purify the residue by column chromatography eluting with 20:1 dichloromethane/methanol to obtain 4-Chloro-2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidine (1100 mg) as a white solid.

4. (3,4-difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine



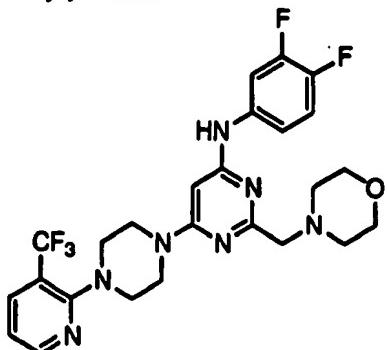
To a de-gassed mixture of 4-chloro-2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidine (100 mg, 0.258 mmol), 3,4-difluoroaniline (37 mg, 0.284 mmol), and 1M (THF) potassium *tert*-butoxide (0.0516 mmol), in dioxane (4mL) under nitrogen add Pd(OAc)₂ (0.01 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.013 mmol). Stir the mixture at 80°C for 16 hours, concentrate, extract with EtOAc. Dry over Na₂SO₄, concentrate under vacuum, and purify by preparative TLC (1:3 hexanes/EtOAc) to give (3,4-difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine.

5. {4-(3,4-difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-methanol



To a solution of (3,4-difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine (40 mg) in dichloromethane (10 mL), add 2 drops of BBr₃. Stir the mixture 1 hour at room temperature and concentrate. Purify by preparative TLC (5:95 MeOH/CH₂Cl₂ eluent) to afford {4-(3,4-difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-methanol.

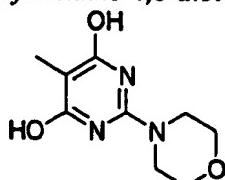
6. (3,4-difluoro-phenyl)-{2-morpholin-4-ylmethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine



- To a cooled solution (0°C) of {4-(3,4-difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-methanol (50 mg, 0.103 mmol), add triethylamine (60 µL, 0.429 mmol) followed by methanesulfonyl chloride (18 µL, 0.236 mmol). Stir the mixture for 1 hour at room temperature then concentrate. Mix the residue with morpholine (100 µL) and N,N-dimethylacetamide (1 mL). Heat the solution at 70°C for 4 hours, and then partition the reaction mixture between saturated aqueous NaCl and EtOAc. Wash the organic layer with water, dry over Na₂SO₄, and concentrate. Purify by preparative TLC (7:93:1 MeOH/CH₂Cl₂/NH₄OH eluent) to yield (3,4-difluoro-phenyl)-{2-morpholin-4-ylmethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine.

C. (3,4-Difluorophenyl)(5-methyl-2-morpholin-4-yl-6-[4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl]pyrimidin-4-yl)amine

1. 5-Methyl-2-morpholin-4-ylpyrimidine-4,6-diol



- Heat a mixture of sodium methoxide in methanol (15 ml, 45 mmol), 20 morpholinoformamidine hydrobromide (6.3 g, 30 mmol) and diethyl methylmalonate (5.22 g, 30 mmol) at 50°C for 2 hours. Cool the mixture and concentrate under reduced pressure. Dissolve the white gum in water and acidify the solution with concentrated sulfuric acid. Collect the resulting white solid by filtration, washed with water and air dry to give the title compound (4.3 g, 68%).

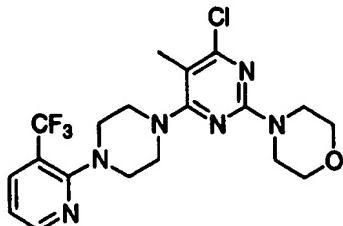
2. 4-(4,6-Dichloro-5-methylpyrimidinyl-2-yl)morpholine



Heat a mixture of 5-methyl-2-morpholin-4-ylpyrimidine-4,6-diol (3.57 g, 17 mmol), *N,N*-diethylaniline (4.37 g, 35 mmol) and phosphorus oxychloride (25 mL) at 90°C for 2 hours.

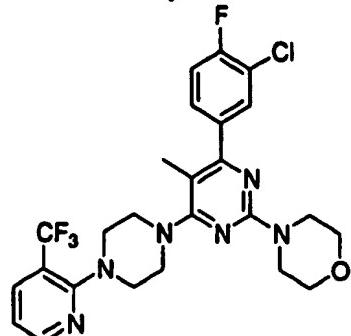
- 5 Remove the excess phosphorus oxychloride by evaporation, add water (100 mL) and extract the solution with ethyl acetate (3 x 100 mL). Wash the combined organics with 1M hydrochloric acid (100 mL), water (100 mL), brine (100 mL), dry (MgSO_4) and concentrate under reduced pressure to give the title compound (3.3 g) which was used without further purification.

10 3. 4-(4-Chloro-5-methyl-6-[4-(3-(trifluoromethyl)(2-pyridyl)piperazinyl]pyrimidin-2-yl)morpholine



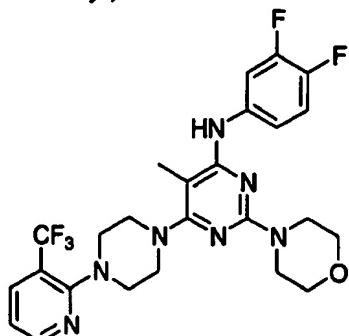
Heat a mixture of 4-(4,6-dichloro-5-methylpyrimidinyl-2-yl)morpholine (496 mg, 2.0 mmol), 4-(6-trifluoromethyl-2-pyridyl)piperazine (462 mg, 2.0 mmol), potassium carbonate (345 mg, 2.5 mmol) and ethanol (10 mL) at 78°C for 8 hours. Cool the mixture, dilute with water (20 mL) and extract with ethyl acetate (3 x 25 mL). Wash the combined organics with brine (25 mL), dry (MgSO_4) and concentrate under reduced pressure. Purify the residue using flash chromatography on silica gel (80% hexane/ 20% ether) to give the title compound (671 mg, 76%).

4. 4-(4-(3-Chloro-4-fluorophenyl)-5-methyl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-2-yl)morpholine



Heat a mixture of 4-(4-chloro-5-methyl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-2-yl)morpholine (66 mg, 0.15 mmol), 3-chloro-4-fluorophenylboronic acid (35 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium(0) (10 mg) and 2M potassium carbonate (0.2 mL) in toluene (3 mL), under a nitrogen atmosphere, at 80°C for 4 hours. Cool the reaction mixture and separate the layers. Extract the aqueous layer with ethyl acetate (3 x 10 mL) and wash the combined organics with 4M sodium hydroxide (10 mL), water (10 mL), brine (10 mL), dry (MgSO_4) and concentrate under reduced pressure. Purify the residue using flash chromatography on silica gel (70% hexane/ 30% ether) to give the title compound (54 mg, 67%). MS 537 (M + 1).

5. (3,4-Difluorophenyl)(5-methyl-2-morpholin-4-yl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-4-yl)amine



Add 3,4-difluoroaniline (26 mg, 0.2 mmol) to a solution of 4-(4-chloro-5-methyl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-2-yl)morpholine (88 mg, 0.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.02 mmol), and (*rac*)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (17 mg, 0.02 mmol) in toluene (2 mL) under nitrogen followed by potassium *tert*-butoxide (45 mg, 0.4 mmol). Stir the mixture at 90°C for 8 hours, dilute with aqueous ammonium chloride, and extract with ethyl acetate (3 x 10 mL). Dry

(MgSO₄) the combined extracts and concentrate under reduced pressure. Purify the residue by flash chromatography on silica gel (60% hexane/ 40% ether) to give the title compound (63 mg, 59%). MS 536 (M + 1).

5

EXAMPLE 3

Representative Substituted Heterocyclic Diarylamine Analogues

Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein. Compounds listed in Table I were prepared using such methods. Mass spectroscopy data is Electrospray MS, obtained in positive ion mode with a 15V or 30V cone voltage, using a Micromass Time-of-Flight LCT, equipped with a Waters 600 pump, Waters 996 photodiode array detector, Gilson 215 autosampler, and a Gilson 841 microinjector. MassLynx (Advanced Chemistry Development, Inc; Toronto, Canada) version 4.0 software was used for data collection and analysis. Sample volume of 1 microliter was injected onto a 50x4.6mm Chromolith SpeedROD C18 column, and eluted using a 2-phase linear gradient at 6ml/min flow rate. Sample was detected using total absorbance count over the 220-340nm UV range. The elution conditions were: Mobile Phase A- 95/5/0.05 Water/Methanol/TFA; Mobile Phase B-5/95/0.025 Water/Methanol/TFA.

Gradient:	<u>Time(min)</u>	<u>%B</u>
20	0	10
	0.5	100
	1.2	100
	1.21	10

The total run time was 2 minutes inject to inject.

In the column labeled K_i in Table I, * indicates that the K_i for the compound, determined 25 as described in Example 5, herein, is 1 micromolar or less.

Table I
Representative Substituted Heterocyclic Diarylamine Analogs

Compound	Name	MS	K _i
1.	(3,4-Difluoro-phenyl)-{2-(2,6-dimethyl-morpholin-4-ylmethyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine		*
2.	(3,4-Difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine	480.2	*
3.	(3,4-Difluoro-phenyl)-{2-morpholin-4-ylmethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine		*
4.	(3,4-Difluoro-phenyl)-{4-[4-(3-methanesulfonyl-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine (R)	546.2	*
5.	(3,4-Difluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine	522.2	*

Compound	Name	MS	K _i
6.	(3-Chloro-phenyl)-{4-[4-(3-chloropyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine	486.1	*
7.	(3-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine	520.2	*
8.	(3-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine	519.2	*
9.	(3-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine	504.2	*
10.	(3-Methoxy-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine	515.2	*
11.	(4-Chloro-phenyl)-{4-[4-(3-chloropyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine	486.1	*

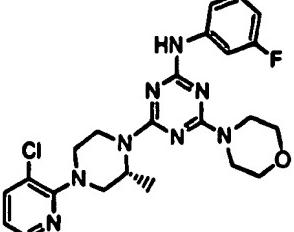
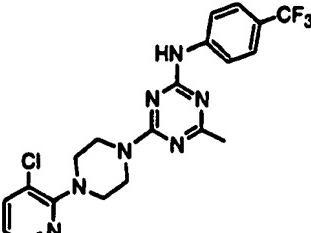
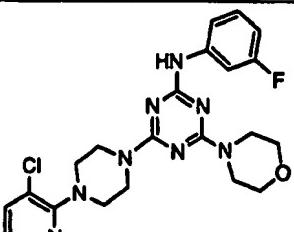
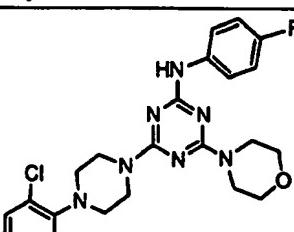
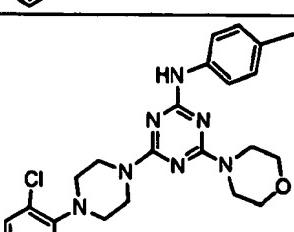
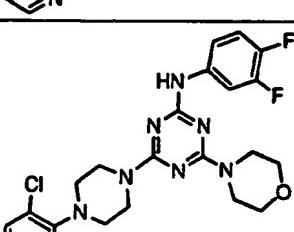
	Compound	Name	MS	K _i
12.		(4-Chlorophenyl)-{4-morpholin-4-yl}-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-amine	520.2	*
13.		(4-Fluorophenyl)-[2-morpholin-4-yl]-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-4-yl-amine	435.2	*
14.		(4-Fluorophenyl)-{4-morpholin-4-yl}-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-amine	504.2	*
15.		(4-Fluorophenyl)-{4-morpholin-4-yl}-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl-amine	503.2	*
16.		(4-Fluorophenyl)-{6-morpholin-4-yl}-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl-amine	503.2	*
17.		(4-Methoxyphenyl)-{4-morpholin-4-yl}-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl-amine	515.2	*

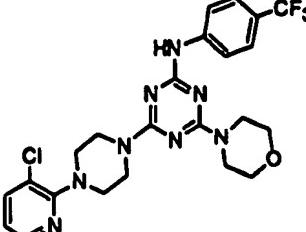
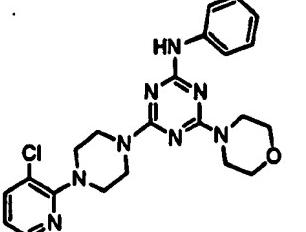
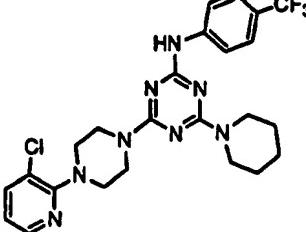
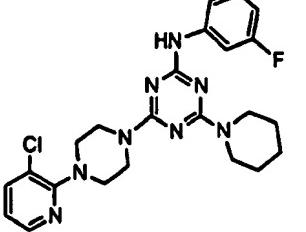
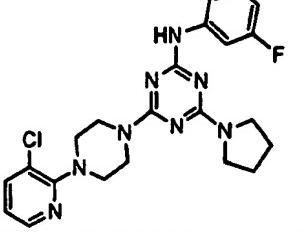
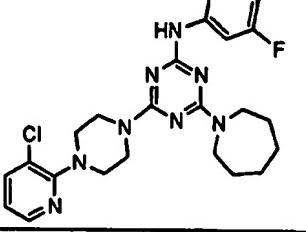
Compound	Name	MS	K _i
18.	(4- <i>tert</i> -Butyl-phenyl)-[4-(4-pyridin-2-yl-piperazin-1-yl)-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-amine	563.3	*
19.	(4- <i>tert</i> -Butyl-phenyl)-[4-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-amine (R)	645.3	*
20.	(4- <i>tert</i> -Butyl-phenyl)-[4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-amine	592.3	*
21.	(4- <i>tert</i> -Butyl-phenyl)-[4-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-amine (R)	611.3	*
22.	(4- <i>tert</i> -Butyl-phenyl)-[4-[4-(3-fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-amine (R)	595.3	*

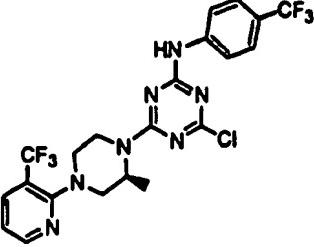
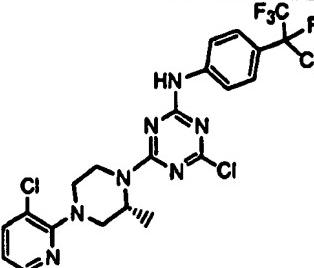
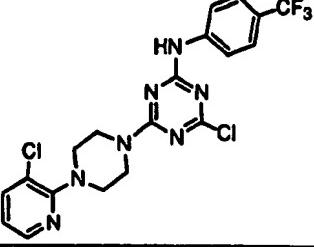
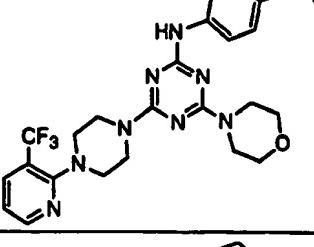
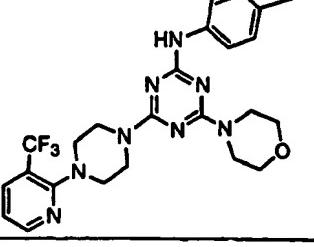
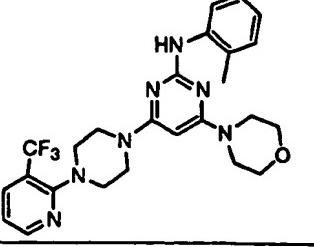
Compound	Name	MS	K _i
23.	(4- <i>tert</i> -Butyl-phenyl)-{4-chloro-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R)	505.2	*
24.	(4- <i>tert</i> -Butyl-phenyl)-{4-chloro-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R)	471.2	*
25.	(4- <i>tert</i> -Butyl-phenyl)-{4-chloro-6-[4-(3-fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R)	455.2	
26.	(4- <i>tert</i> -Butyl-phenyl)-{6-[4-(3-chloropyridin-2-yl)-2-methyl-piperazin-1-yl]-pyrimidin-4-yl}-amine (R)	436.2	*
27.	[4-[2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-{4-trifluoromethyl-phenyl}-amine (R)	657.2	*

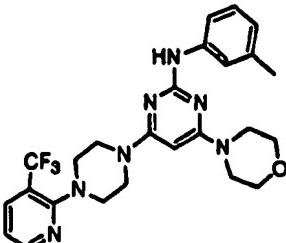
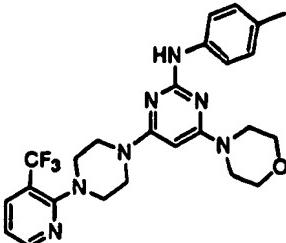
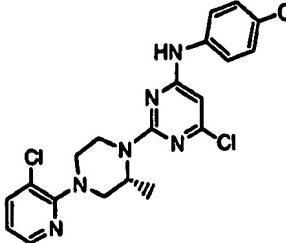
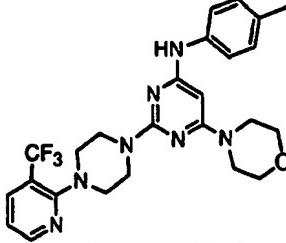
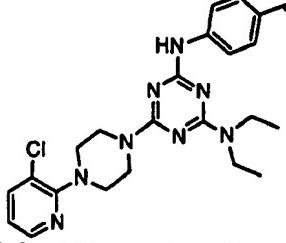
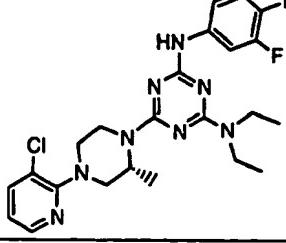
	Compound	Name	MS	K _i
28.		[4-[2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(4-trifluoromethyl-phenyl)-[1,3,5]triazin-2-yl]-4-trifluoromethyl-phenyl)-amine (S)	627.2	*
29.		[4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-4-trifluoromethyl-phenyl)-amine (R)	623.2	*
30.		[4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2,4-dimethoxy-phenyl)-[1,3,5]triazin-2-yl]-4-trifluoromethyl-phenyl)-amine		*
31.		[4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(4-isopropyl-phenyl)-[1,3,5]triazin-2-yl]-4-trifluoromethyl-phenyl)-amine		*
32.		[4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-(2-methyl-pyrrolidin-1-yl)-[1,3,5]triazin-2-yl]-3-fluorophenyl)-amine	468.2	*
33.		[4-[4-(3-Fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-4-trifluoromethyl-phenyl)-amine (R)	607.2	*

Compound	Name	MS	K _i
34.	{2-Diethylaminomethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-(3,4-difluoro-phenyl)-amine		*
35.	{4-(2-Chloro-phenyl)-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine (S)	593.2	*
36.	{4-(4-Butyl-phenyl)-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine		*
37.	{4-(3,4-Difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-methanol		*
38.	{4,6-Bis-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine	630.2	*
39.	{4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3,4-difluoro-phenyl)-amine (R)	502.2	*

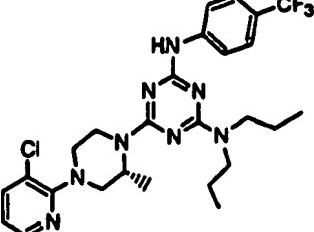
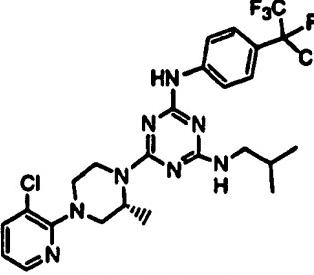
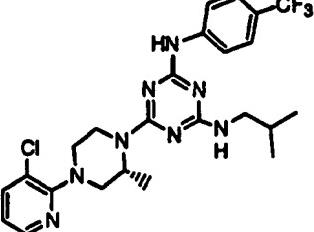
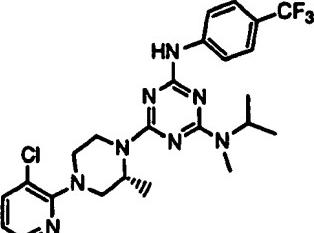
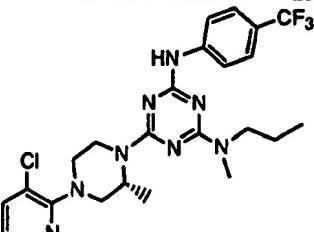
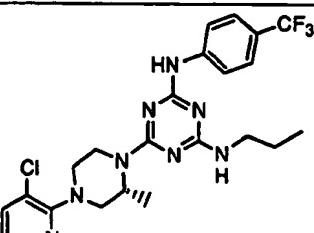
Compound	Name	MS	K _i	
40.		{4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(3-fluorophenyl)-amine	484.2	*
41.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-methyl-[1,3,5]triazin-2-yl)-(4-trifluoromethylphenyl)-amine	449.1	*
42.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(3-fluoro-phenyl)-amine	470.2	*
43.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(4-fluoro-phenyl)-amine	470.2	*
44.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-p-tolyl-amine	466.2	*
45.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(3,4-difluorophenyl)-amine	488.2	*

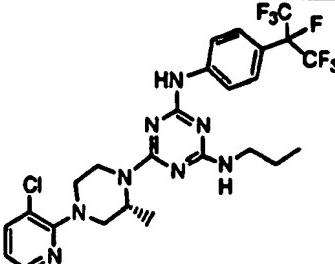
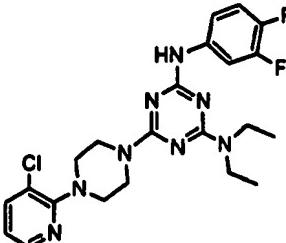
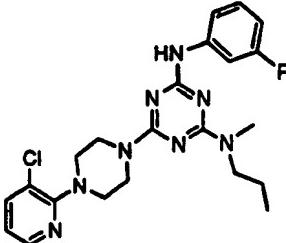
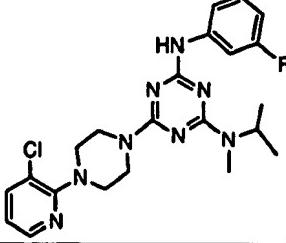
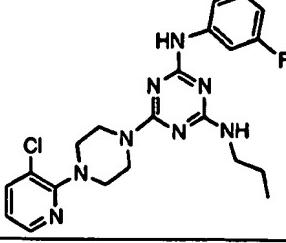
Compound	Name	MS	K _i	
46.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(4-trifluoromethyl-phenyl)-amine	520.2	*
47.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-phenyl-amine	452.2	*
48.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-(4-trifluoromethyl-phenyl)-amine	518.2	*
49.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-(3-fluoro-phenyl)-amine	468.2	*
50.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-pyrrolidin-1-yl-[1,3,5]triazin-2-yl)-(3-fluoro-phenyl)-amine	454.2	*
51.		{4-Azepan-1-yl-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-(3-fluoro-phenyl)-amine	482.2	*

Compound	Name	MS	K _i	
52.		{4-Chloro-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-(4-trifluoromethyl-phenyl)-amine (S)	517.1	*
53.		{4-Chloro-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl)-(4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl)-amine (R)	583.1	*
54.		{4-Chloro-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-(4-trifluoromethyl-phenyl)-amine	469.1	*
55.		{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-(4-trifluoromethyl-phenyl)-amine	554.2	*
56.		{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-p-tolyl-amine	500.	*
57.		{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl)-o-tolyl-amine	499.2	*

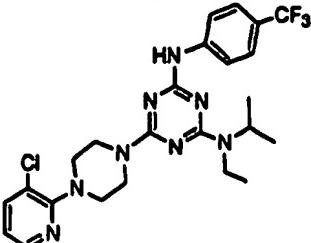
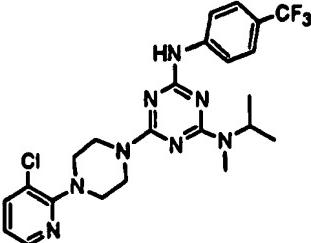
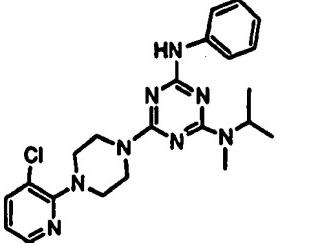
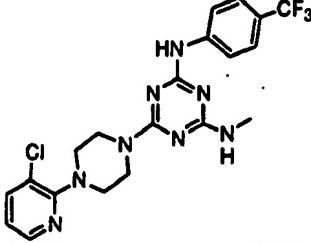
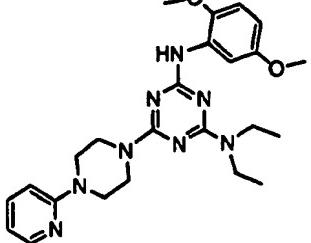
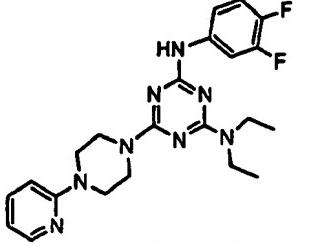
Compound	Name	MS	K _i	
58.		{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-m-tolyl-amine	499.2	*
59.		{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-p-tolyl-amine	499.2	*
60.		{6-Chloro-2-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-pyrimidin-4-yl}-{4-trifluoromethyl-phenyl}-amine (R)	482.1	*
61.		{6-Morpholin-4-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-p-tolyl-amine	499.2	*
62.		4-[4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-diethylamino-[1,3,5]triazin-2-ylamino]-benzonitrile	448.2	*
63.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3,4-difluoro-phenyl)-N',N'-diethyl-[1,3,5]triazine-2,4-diamine (R)	488.2	*

Compound	Name	MS	K _i
64.			*
65.			*
66.		582.2	*
67.		622.2	*
68.		492.2	*
69.		492.2	*

Compound	Name	MS	K _i	
70.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dipropyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	548.2	*
71.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isobutyl-N'-(4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl)-[1,3,5]triazine-2,4-diamine (R)	620.2	*
72.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isobutyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)		*
73.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	520.2	*
74.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-methyl-N-propyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	520.2	*
75.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-propyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	506.2	*

Compound	Name	MS	K _i
76.		606.2	*
77.		474.2	*
78.		456.2	*
79.		428.2	*
80.		456.2	*
81.		442.2	*

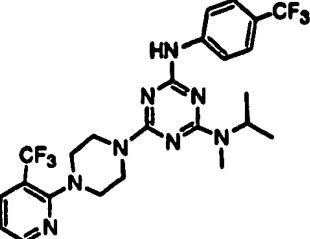
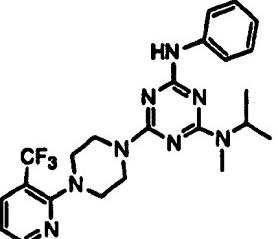
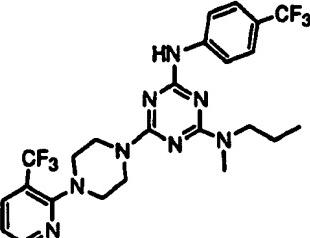
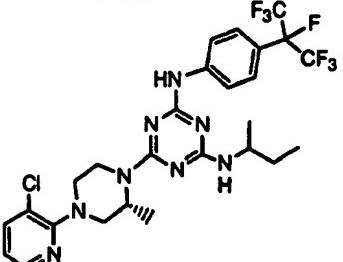
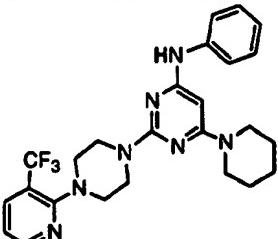
Compound	Name	MS	K _i
82.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine	456.2 *
83.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3-methoxy-phenyl)-[1,3,5]triazine-2,4-diamine	468.2 *
84.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(4-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine	456.2 *
85.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	478.2 *
86.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N'-(3-fluoro-phenyl)-N-methyl-[1,3,5]triazine-2,4-diamine	442.2 *
87.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N'-(3-fluoro-phenyl)-N-isopropyl-[1,3,5]triazine-2,4-diamine	470.2 *

Compound	Name	MS	K _i
88.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N-isopropyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	520.2 *
89.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	506.2 *
90.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-isopropyl-N-methyl-N'-phenyl-[1,3,5]triazine-2,4-diamine	438.2 *
91.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	464.1 *
92.		N-(2,5-Dimethoxy-phenyl)-N',N'-diethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine	449.3 *
93.		N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine	440.2 *

	Compound	Name	MS	K _i
94.		N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine (R)	522.2	*
95.		N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-[4-(3-methanesulfonyl-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine (R)	532.2	*
96.		N-(3-Chloro-phenyl)-6-[4-(3-chloropyridin-2-yl)-piperazin-1-yl]-N',N'-diethyl-[1,3,5]triazine-2,4-diamine	472.2	*
97.		N-(3-Methyl-butyl)-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (S)	568.2	*
98.		N-(3-Methyl-butyl)-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	554.2	*
99.		N,N-Diallyl-6-[4-(3-chloropyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	544.2	*

Compound	Name	MS	K _i
100.	N,N-Dibutyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	576.3	*
101.	N,N-Diethyl-N'-(4-fluoro-phenyl)-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine	422.2	*
102.	N,N-Dimethyl-6-(4-phenyl-piperazin-1-yl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	443.2	*
103.	N,N-Dimethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	444.2	*
104.	N,N-Dimethyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	512.2	*
105.	N,N-Dimethyl-N'-phenyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	444.2	*

	Compound	Name	MS	K _i
106.		N-Benzyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)		*
107.		N-Butyl-6-[4-(2-chloro-phenyl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R)		*
108.		N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	520.2	*
109.		N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	534.2	*
110.		N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	534.2	*
111.		N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-N'-(3-fluoro-phenyl)-N-methyl-[1,3,5]triazine-2,4-diamine	470.2	*

Compound	Name	MS	K _i
112. 	N-Isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	540.2	*
113. 	N-Isopropyl-N-methyl-N'-(4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine	472.2	*
114. 	N-Methyl-N-propyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	540.2	*
115. 	N-sec-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl)-[1,3,5]triazine-2,4-diamine (R)	620.2	*
116. 	Phenyl-(6-piperidin-1-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl)-amine	483.2	*

EXAMPLE 4
VR1-Transfected Cells and Membrane Preparations

This Example illustrates the preparation of VR1-transfected cells and membrane preparations for use in binding assays (Example 5) and functional assays (Example 6).

A cDNA encoding full length human capsaicin receptor (SEQ ID NO:1, 2 or 3 of U.S. Patent No. 6,482,611) was subcloned in the plasmid pBK-CMV (Stratagene, La Jolla, CA) for recombinant expression in mammalian cells.

Human embryonic kidney (HEK293) cells were transfected with the pBK-CMV expression construct encoding the full length human capsaicin receptor using standard methods. The transfected cells were selected for two weeks in media containing G418 (400 µg/ml) to obtain a pool of stably transfected cells. Independent clones were isolated from this pool by limiting dilution to obtain clonal stable cell lines for use in subsequent experiments.

For radioligand binding experiments, cells were seeded in T175 cell culture flasks in media without antibiotics and grown to approximately 90% confluence. The flasks were then washed with PBS and harvested in PBS containing 5 mM EDTA. The cells were pelleted by gentle centrifugation and stored at -80°C until assayed.

Previously frozen cells were disrupted with the aid of a tissue homogenizer in ice-cold HEPES homogenization buffer (5mM KCl, 5, 5.8mM NaCl, 0.75mM CaCl₂, 2mM MgCl₂, 320 mM sucrose, and 10 mM HEPES pH 7.4). Tissue homogenates were first centrifuged for 10 minutes at 1000 x g (4°C) to remove the nuclear fraction and debris, and then the supernatant from the first centrifugation is further centrifuged for 30 minutes at 35,000 x g (4°C) to obtain a partially purified membrane fraction. Membranes were resuspended in the HEPES homogenization buffer prior to the assay. An aliquot of this membrane homogenate is used to determine protein concentration via the Bradford method (BIO-RAD Protein Assay Kit, #500-0001, BIO-RAD, Hercules, CA).

EXAMPLE 5

Capsaicin Receptor Binding Assay

This Example illustrates a representative assay of capsaicin receptor binding that may be used to determine the binding affinity of compounds for the capsaicin (VR1) receptor.

Binding studies with [³H] Resiniferatoxin (RTX) are carried out essentially as described by Szallasi and Blumberg (1992) *J. Pharmacol. Exp. Ter.* 262:883-888. In this protocol, non-specific RTX binding is reduced by adding bovine alpha₁ acid glycoprotein (100 µg per tube) after the binding reaction has been terminated.

[³H] RTX (37 Ci/mmol) is synthesized by and obtained from the Chemical Synthesis and Analysis Laboratory, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD. [³H] RTX may also be obtained from commercial vendors (e.g., Amersham Pharmacia Biotech, Inc.; Piscataway, NJ).

5 The membrane homogenate of Example 4 is centrifuged as before and resuspended to a protein concentration of 333 μ g/ml in homogenization buffer. Binding assay mixtures are set up on ice and contain [³H]RTX (specific activity 2200 mCi/ml), 2 μ l non-radioactive test compound, 0.25 mg/ml bovine serum albumin (Cohn fraction V), and 5×10^4 - 1×10^5 VR1-transfected cells. The final volume is adjusted to 500 μ l (for competition binding assays) or
10 1,000 μ l (for saturation binding assays) with the ice-cold HEPES homogenization buffer solution (pH 7.4) described above. Non-specific binding is defined as that occurring in the presence of 1 μ M non-radioactive RTX (Alexis Corp.; San Diego, CA). For saturation binding, [³H]RTX is added in the concentration range of 7 - 1,000 pM, using 1 to 2 dilutions. Typically 11 concentration points are collected per saturation binding curve.

15 Competition binding assays are performed in the presence of 60 pM [³H]RTX and various concentrations of test compound. The binding reactions are initiated by transferring the assay mixtures into a 37°C water bath and are terminated following a 60 minute incubation period by cooling the tubes on ice. Membrane-bound RTX is separated from free, as well as any alpha₁-acid glycoprotein-bound RTX, by filtration onto WALLAC glass fiber filters (PERKIN-
20 ELMER, Gaithersburg, MD) which were pre-soaked with 1.0% PEI (polyethyleneimine) for 2 hours prior to use. Filters are allowed to dry overnight then counted in a WALLAC 1205 BETA PLATE counter after addition of WALLAC BETA SCINT scintillation fluid.

25 Equilibrium binding parameters are determined by fitting the allosteric Hill equation to the measured values with the aid of the computer program FIT P (Biosoft, Ferguson, MO) as described by Szallasi, *et al.* (1993) *J. Pharmacol. Exp. Ther.* 266:678-683. Compounds provided herein generally exhibit K_i values for capsaicin receptor of less than 1 μ M, 100 nM, 50 nM, 25 nM, 10 nM, or 1nM in this assay.

EXAMPLE 6
Calcium Mobilization Assay

This Example illustrates a representative calcium mobilization assay for use in monitoring the response of cells expressing capsaicin receptor to capsaicin and other vanilloid ligands of the capsaicin receptor, as well as for evaluating test compounds for agonist and antagonist activity.

Cells transfected with expression plasmids (as described in Example 4) and thereby expressing human capsaicin receptor are seeded and grown to 70-90% confluence in FALCON black-walled, clear-bottomed 96-well plates (#3904, BECTON-DICKINSON, Franklin Lakes, NJ). The culture medium is emptied from the 96 well plates and FLUO-3 AM calcium sensitive dye (Molecular Probes, Eugene, OR) is added to each well (dye solution: 1 mg FLUO-3 AM, 440 μ L DMSO and 440 μ l 20% pluronic acid in DMSO, diluted 1:250 in Krebs-Ringer HEPES (KRH) buffer (25 mM HEPES, 5 mM KCl, 0.96 mM NaH₂PO₄, 1 mM MgSO₄, 2 mM CaCl₂, 5 mM glucose, 1 mM probenecid, pH 7.4), 50 μ l diluted solution per well). Plates are covered with aluminum foil and incubated at 37°C for 1-2 hours in an environment containing 5% CO₂. After the incubation, the dye is emptied from the plates, and the cells are washed once with KRH buffer, and resuspended in KRH buffer.

Agonist (e.g., olvanil, capsaicin, or RTX)-induced calcium mobilization is monitored using either FLUOROSKAN ASCENT (Labsystems, Franklin, MA) or FLIPR (fluorometric imaging plate reader system, Molecular Devices, Sunnyvale, CA) instruments. Varying concentrations of the antagonists ruthenium red or capsazepine (RBI; Natick, MA) are added to cells concurrently with agonist (e.g., 25-50 nM capsaicin). For agonist-induced calcium responses, data obtained between 30 and 60 seconds after agonist application are used to generate the IC₅₀ values. KALEIDAGRAPH software (Synergy Software, Reading, PA) is used 25 to fit the data to the equation:

$$y=a*(1/(1+(b/x)^c))$$

to determine the IC₅₀ for the response. In this equation, y is the maximum fluorescence signal, x is the concentration of the agonist or antagonist, a is the E_{max}, b corresponds to the IC₅₀ value and c is the Hill coefficient.

To measure the ability of a test compound to antagonize (inhibit) the response of cells expressing capsaicin receptors to capsaicin or other vanilloid agonist, the IC₅₀ of capsaicin is first

determined. An additional 20 μ l of KRH buffer and 1 μ l DMSO is added to each well of cells, prepared as described above. 100 μ l capsaicin in KRH buffer is automatically transferred by the FLIPR instrument to each well. An 8-point concentration response curve, with final capsaicin concentrations of 1 nM to 3 μ M, is used to determine capsaicin IC₅₀.

5 Test compounds are dissolved in DMSO, diluted in 20 μ l KRH buffer so that the final concentration of test compounds in the assay well is between 1 μ M and 5 μ M, and added to cells prepared as described above. The 96 well plates containing prepared cells and test compounds are incubated in the dark, at room temperature for 0.5 to 6 hours. It is important that the incubation not continue beyond 6 hours. Just prior to determining the fluorescence response, 100
10 μ l capsaicin in KRH buffer at twice the IC₅₀ concentration determined from the concentration response curve is automatically added by the FLIPR instrument to each well of the 96 well plate for a final sample volume of 200 μ l and a final capsaicin concentration equal to the IC₅₀. The final concentration of test compounds in the assay wells is between 1 μ M and 5 μ M. Typically cells exposed to one IC₅₀ of capsaicin exhibit a fluorescence response of about 10,000 Relative
15 Fluorescence Units. Antagonists of the capsaicin receptor decrease this response by at least about 20%, preferably by at least about 50%, and most preferably by at least 80% as compared to matched control. The concentration of antagonist required to provide a 50% decrease is the IC₅₀ for the antagonist, and is preferably below 1 micromolar, 100 nanomolar, 10 nanomolar or 1 nanomolar.

20 The ability of a compound to act as an agonist of the capsaicin receptor is determined by measuring the fluorescence response of cells expressing capsaicin receptors, using the methods described above, in the absence of capsaicin, RTX, or other capsaicin receptor agonists. Compounds that cause cells to exhibit fluorescence above background are capsaicin receptor agonists. Certain preferred compounds of the present invention are antagonists that are
25 essentially free of agonist activity as demonstrated by the absence of detectable agonist activity in such an assay at compound concentrations below 4 nM, more preferably at concentrations below 10 μ M and most preferably at concentrations less than or equal to 100 μ M.

EXAMPLE 7
Microsomal *in vitro* half-life

This Example illustrates the evaluation of compound half-life values ($t_{1/2}$ values) using a representative liver microsomal half-life assay.

- 5 Pooled human liver microsomes are obtained from XenoTech LLC, 3800 Cambridge St., Kansas City, Kansas 66103 (catalog # H0610). Such liver microsomes may also be obtained from In Vitro Technologies (Baltimore, MD) or Tissue Transformation Technologies (Edison, NJ). Six test reactions are prepared, each containing 25 μ l microsomes, 5 μ l of a 100 μ M solution of test compound, and 399 μ l 0.1 M phosphate buffer (19 mL 0.1 M NaH₂PO₄, 81 mL 10 0.1 M Na₂HPO₄, adjusted to pH 7.4 with H₃PO₄). A seventh reaction is prepared as a positive control containing 25 μ l microsomes, 399 μ l 0.1 M phosphate buffer, and 5 μ l of a 100 μ M solution of a compound with known metabolic properties (e.g., DIAZEPAM or CLOZAPINE). Reactions are preincubated at 39°C for 10 minutes.

- CoFactor Mixture is prepared by diluting 16.2 mg NADP and 45.4 mg Glucose-6-phosphate in 4 mL 100 mM MgCl₂. Glucose-6-phosphate dehydrogenase solution is prepared by diluting 214.3 μ l glucose-6-phosphate dehydrogenase suspension (Boehringer-Manheim catalog no. 0737224, distributed by Roche Molecular Biochemicals, Indianapolis, IN) into 1285.7 μ l distilled water. 71 μ l Starting Reaction Mixture (3 mL CoFactor Mixture; 1.2 mL Glucose-6-phosphate dehydrogenase solution) is added to 5 of the 6 test reactions and to the positive 15 control. 71 μ l 100 mM MgCl₂ is added to the sixth test reaction, which is used as a negative control. At each time point (0, 1, 3, 5, and 10 minutes), 75 μ l of each reaction mix is pipetted into a well of a 96-well deep-well plate containing 75 μ l ice-cold acetonitrile. Samples are vortexed and centrifuged 10 minutes at 3500 rpm (Sorval T 6000D centrifuge, H1000B rotor). 20 75 μ l of supernatant from each reaction is transferred to a well of a 96-well plate containing 150 μ l of a 0.5 μ M solution of a compound with a known LCMS profile (internal standard) per well. LCMS analysis of each sample is carried out and the amount of unmetabolized test compound is 25 measured as AUC, compound concentration vs. time is plotted, and the $t_{1/2}$ value of the test compound is extrapolated.

- Preferred compounds of the present invention exhibit *in vitro* $t_{1/2}$ values of greater than 10 30 minutes and less than 4 hours, preferably between 30 minutes and 1 hour, in human liver microsomes.

EXAMPLE 8
MDCK Toxicity Assay

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

- 5 1 µL of test compound is added to each well of a clear bottom 96-well plate (PACKARD, Meriden, CT) to give final concentration of compound in the assay of 10 micromolar, 100 micromolar or 200 micromolar. Solvent without test compound is added to control wells.

MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a concentration of 0.1×10^6 cells/ml with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 µL of diluted cells is added to each well, except for five standard curve control wells that contain 100 µL of warm medium without cells. The plate is then incubated at 37°C under 95% O₂, 5% CO₂ for 2 hours with constant shaking. After 15 incubation, 50 µL of mammalian cell lysis solution is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes.

Compounds causing toxicity will decrease ATP production, relative to untreated cells. The PACKARD, (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit, product no. 20 6016941, is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 mls of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 25 µL of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM and 12.5 nM. PACKARD substrate solution (50 µL) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes. A white 30 PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in the dark for 10 minutes. Luminescence is then measured at 22°C using a luminescence counter (e.g., PACKARD TOPCOUNT Microplate Scintillation and

Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μ M of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μ M concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

EXAMPLE 9
Dorsal Root Ganglion Cell Assay

This Example illustrates a representative dorsal root ganglion cell assay for evaluating VR1 antagonist activity of a compound.

DRG are dissected from neonatal rats, dissociated and cultured using standard methods (Aguayo and White (1992) *Brain Research* 570:61-67). After 48 hour incubation, cells are washed once and incubated for 30-60 minutes with the calcium sensitive dye Fluo 4 AM (2.5-10 ug/ml; TefLabs, Austin, TX). Cells are then washed once, and various concentrations of compound is added to the cells. Addition of capsaicin to the cells results in a VR1-dependent increase in intracellular calcium levels which is monitored by a change in Fluo-4 fluorescence with a fluorometer. Data are collected for 60-180 seconds to determine the maximum fluorescent signal. Fluorescent signal is then plotted as a function of compound concentration to identify the concentration required to achieve a 50% inhibition of the capsaicin-activated response, or IC₅₀. Antagonists of the capsaicin receptor preferably have an IC₅₀ below 1 micromolar, 100 nanomolar, 10 nanomolar or 1 nanomolar.

EXAMPLE 10
Animal Models for Determining Pain Relief

This Example illustrates representative methods for assessing the degree of pain relief provided by a compound.

A. Pain Relief Testing

The following methods may be used to assess pain relief.

MECHANICAL ALLODYNIA

Mechanical allodynia (an abnormal response to an innocuous stimulus) is assessed essentially as described by Chaplan *et al.* (1994) *J. Neurosci. Methods* 53:55-63 and Tal and Eliav (1998) *Pain* 64(3):511-518. A series of von Frey filaments of varying rigidity (typically 8-

- 5 14 filaments in a series) are applied to the plantar surface of the hind paw with just enough force to bend the filament. The filaments are held in this position for no more than three seconds or until a positive allodynic response is displayed by the rat. A positive allodynic response consists of lifting the affected paw followed immediately by licking or shaking of the paw. The order and frequency with which the individual filaments are applied are determined by using Dixon up-
10 down method. Testing is initiated with the middle hair of the series with subsequent filaments being applied in consecutive fashion, ascending or descending, depending on whether a negative or positive response, respectively, is obtained with the initial filament.

Compounds are effective in reversing or preventing mechanical allodynia-like symptoms if rats treated with such compounds require stimulation with a Von Frey filament of higher
15 rigidity strength to provoke a positive allodynic response as compared to control untreated or vehicle treated rats. Alternatively, or in addition, testing of an animal in chronic pain may be done before and after compound administration. In such an assay, an effective compound results in an increase in the rigidity of the filament needed to induce a response after treatment, as compared to the filament that induces a response before treatment or in an animal that is also in
20 chronic pain but is left untreated or is treated with vehicle. Test compounds are administered before or after onset of pain. When a test compound is administered after pain onset, testing is performed 10 minutes to three hours after administration.

MECHANICAL HYPERALGESIA

Mechanical hyperalgesia (an exaggerated response to painful stimulus) is tested essentially as described by Koch *et al.* (1996) *Analgesia* 2(3):157-164. Rats are placed in
25 individual compartments of a cage with a warmed, perforated metal floor. Hind paw withdrawal duration (*i.e.*, the amount of time for which the animal holds its paw up before placing it back on the floor) is measured after a mild pinprick to the plantar surface of either hind paw.

Compounds produce a reduction in mechanical hyperalgesia if there is a statistically
30 significant decrease in the duration of hindpaw withdrawal. Test compound may be

administered before or after onset of pain. For compounds administered after pain onset, testing is performed 10 minutes to three hours after administration.

THERMAL HYPERALGESIA

- Thermal hyperalgesia (an exaggerated response to noxious thermal stimulus) is measured
- 5 essentially as described by Hargreaves *et al.* (1988) *Pain*. 32(1):77-88. Briefly, a constant radiant heat source is applied the animals' plantar surface of either hind paw. The time to withdrawal (*i.e.*, the amount of time that heat is applied before the animal moves its paw), otherwise described as thermal threshold or latency, determines the animal's hind paw sensitivity to heat.
- 10 Compounds produce a reduction in thermal hyperalgesia if there is a statistically significant increase in the time to hindpaw withdrawal (*i.e.*, the thermal threshold to response or latency is increased). Test compound may be administered before or after onset of pain. For compounds administered after pain onset, testing is performed 10 minutes to three hours after administration.

15 **B. Pain Models**

Pain may be induced using any of the following methods, to allow testing of analgesic efficacy of a compound. In general, compounds provided herein result in a statistically significant reduction in pain as determined by at least one of the previously described testing methods, using male SD rats and at least one of the following models.

20 **ACUTE INFLAMMATORY PAIN MODEL**

Acute inflammatory pain is induced using the carrageenan model essentially as described by Field *et al.* (1997) *Br. J. Pharmacol.* 121(8):1513-1522. 100-200 µl of 1-2% carrageenan solution is injected into the rats' hind paw. Three to four hours following injection, the animals' sensitivity to thermal and mechanical stimuli is tested using the methods described above. A

25 test compound (0.01 to 50 mg/kg) is administered to the animal, prior to testing, or prior to injection of carrageenan. The compound can be administered orally or through any parenteral route, or topically on the paw. Compounds that relieve pain in this model result in a statistically significant reduction in mechanical allodynia and/or thermal hyperalgesia.

CHRONIC INFLAMMATORY PAIN MODEL

- 30 Chronic inflammatory pain is induced using one of the following protocols:

1. Essentially as described by Bertorelli *et al.* (1999) *Br. J. Pharmacol.* 128(6):1252-1258, and Stein *et al.* (1998) *Pharmacol. Biochem. Behav.* 31(2):455-51, 200 µl Complete Freund's Adjuvant (0.1 mg heat killed and dried *M. Tuberculosis*) is injected to the rats' hind paw: 100 µl into the dorsal surface and 100 µl into the plantar surface.
- 5 2. Essentially as described by Abbadie *et al.* (1994) *J Neurosci.* 14(10):5865-5871 rats are injected with 150 µl of CFA (1.5 mg) in the tibio-tarsal joint.

Prior to injection with CFA in either protocol, an individual baseline sensitivity to mechanical and thermal stimulation of the animals' hind paws is obtained for each experimental animal.

- 10 Following injection of CFA, rats are tested for thermal hyperalgesia, mechanical allodynia and mechanical hyperalgesia as described above. To verify the development of symptoms, rats are tested on days 5, 6, and 7 following CFA injection. On day 7, animals are treated with a test compound, morphine or vehicle. An oral dose of morphine of 1-5 mg/kg is suitable as positive control. Typically, a dose of 0.01-50 mg/kg of test compound is used.
- 15 Compounds can be administered as a single bolus prior to testing or once or twice or three times daily, for several days prior to testing. Drugs are administered orally or through any parenteral route, or applied topically to the animal.

Results are expressed as Percent Maximum Potential Efficacy (MPE). 0% MPE is defined as analgesic effect of vehicle, 100% MPE is defined as an animal's return to pre-CFA 20 baseline sensitivity. Compounds that relieve pain in this model result in a MPE of at least 30%.

CHRONIC NEUROPATHIC PAIN MODEL

Chronic neuropathic pain is induced using the chronic constriction injury (CCI) to the rat's sciatic nerve essentially as described by Bennett and Xie (1988) *Pain* 33:87-107. Rats are anesthetized (e.g. with an intraperitoneal dose of 50-65 mg/kg pentobarbital with additional 25 doses administered as needed). The lateral aspect of each hind limb is shaved and disinfected. Using aseptic technique, an incision is made on the lateral aspect of the hind limb at the mid thigh level. The biceps femoris is bluntly dissected and the sciatic nerve is exposed. On one hind limb of each animal, four loosely tied ligatures are made around the sciatic nerve approximately 1-2 mm apart. On the other side the sciatic nerve is not ligated and is not 30 manipulated. The muscle is closed with continuous pattern and the skin is closed with wound

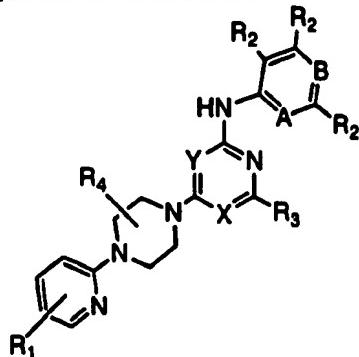
clips or sutures. Rats are assessed for mechanical allodynia, mechanical hyperalgesia and thermal hyperalgesia as described above.

Compounds that relieve pain in this model result in a statistically significant reduction in mechanical allodynia, mechanical hyperalgesia and/or thermal hyperalgesia when administered

- 5 (0.01-50 mg/kg, orally, parenterally or topically) immediately prior to testing as a single bolus, or for several days: once or twice or three times daily prior to testing.

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A and B are independently CR_2 or N ;

X and Y are independently CR_x or N ;

R_x is independently chosen at each occurrence from hydrogen, C_1 - C_6 alkyl and cyano;

R_1 represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkyl ether, C_2 - C_6 alkanoyl, C_3 - C_6 alkanone, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, mono- and di-(C_1 - C_6 alkyl)amino, C_1 - C_6 alkylsulfonyl, mono- and di-(C_1 - C_6 alkyl)sulfonamido, and mono- and di-(C_1 - C_6 alkyl)aminocarbonyl;

Each R_2 is:

(i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_2 - C_6 alkyl ether, C_2 - C_6 alkanoyl, C_3 - C_6 alkanone, mono- and di-(C_1 - C_6 alkyl)amino, C_1 - C_6 alkylsulfonyl, mono- and di-(C_1 - C_6 alkyl)sulfonamido, and mono- and di-(C_1 - C_6 alkyl)aminocarbonyl; or

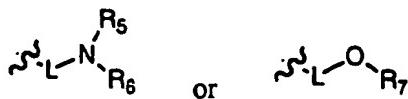
(ii) joined to an adjacent R_2 to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C_1 - C_6 alkyl;

R_3 is selected from:

(i) hydroxy, halogen and C_1 - C_6 haloalkyl;

(ii) C_1 - C_6 alkyl, phenyl and pyridyl; and

(iii) groups of the formula



wherein

L is a bond or C_1 - C_6 alkyl;

R_5 and R_6 are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

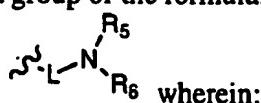
R₄ represents from 0 to 2 methyl substituents.

2. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein R₁ represents from 0 to 2 substituents independently chosen from halogen, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

3. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein R₁ represents one substituent located *ortho* to the point of attachment.

4. A compound or pharmaceutically acceptable form thereof according to claim 3, wherein R₁ is fluoro, chloro, cyano, methyl, trifluoromethyl or methylsulfonyl.

5. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein R₃ is a group of the formula:



L is a bond or C₁-C₄alkyl; and

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₆alkyl and C₁-C₆alkenyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl;

wherein each of which alkyl, alkenyl and heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, amino, hydroxy, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₄alkyl)amino.

6. A compound or pharmaceutically acceptable form thereof according to claim 5, wherein R₃ is di(C₁-C₄alkyl)amino.

7. A compound or pharmaceutically acceptable form thereof according to claim 5, wherein R₃ is pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl or azepanyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, amino, hydroxy and C₁-C₄alkyl.

8. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein R₃ is a group of the formula:



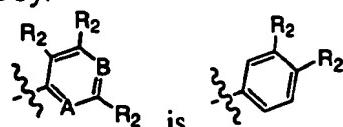
L is a bond or C₁-C₄alkyl; and

R₇ is hydrogen, C₁-C₆alkyl or phenyl(C₀-C₆alkyl), wherein each alkyl and phenylalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, C₁-C₄alkyl, C₁-C₆haloalkyl and C₁-C₆alkoxy.

9. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein each R₂ is independently chosen from hydrogen, amino, cyano, halogen, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

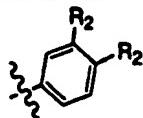
10. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein A and B are CR₂.

11. A compound or pharmaceutically acceptable form thereof according to claim 10, wherein the group represented by:

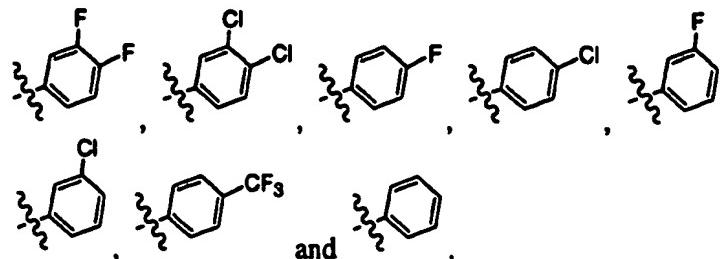


12. A compound or pharmaceutically acceptable form thereof according to claim 11,

wherein:



is selected from:

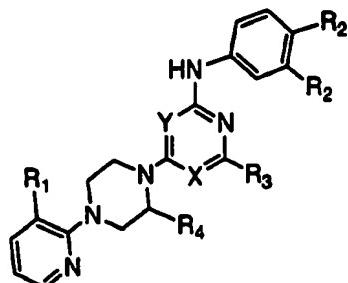


and

13. A compound or pharmaceutically acceptable form thereof according to claim 1,
wherein X is N.

14. A compound or pharmaceutically acceptable form thereof according to claim 1,
wherein Y is N.

15. A compound according to claim 1, having the formula:



wherein R4 is hydrogen or methyl.

16. A compound according to claim 15, wherein:

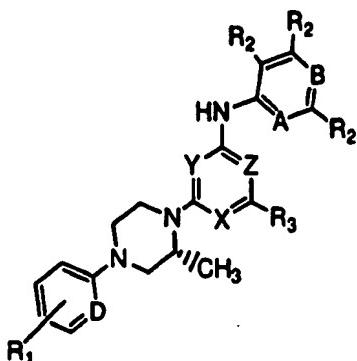
R1 is fluoro, chloro, cyano, methyl or trifluoromethyl;

each R2 is independently chosen from hydrogen, halogen, cyano and C1-C4haloalkyl; and

R3 is mono- or di-(C1-C6alkyl)amino, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl or benzyloxy, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, amino, hydroxyl, C1-C4alkyl, cyano, C1-C4alkoxy, C1-C4haloalkyl and mono- and di-(C1-C6alkyl)amino.

17. A compound or pharmaceutically acceptable form thereof according to claim 1,
wherein the compound exhibits no detectable agonist activity an *in vitro* assay of capsaicin
receptor agonism.

18. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

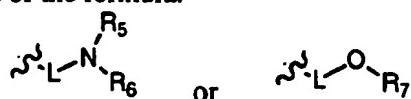
R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

- (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or
- (ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl; and

R₃ is selected from:

- (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
- (ii) C₁-C₆alkyl, phenyl and pyridyl; and
- (iii) groups of the formula:



wherein

L is a bond or C₁-C₆alkyl;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₈alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl.

19. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein D is N.

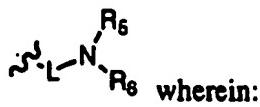
20. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein Z is N.

21. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₁ represents from 0 to 2 substituents independently chosen from halogen, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

22. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₁ represents one substituent located *ortho* to the point of attachment.

23. A compound or pharmaceutically acceptable form thereof according to claim 22, wherein R₁ is fluoro, chloro, cyano, methyl, trifluoromethyl or methylsulfonyl.

24. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₃ is a group of the formula:



L is a bond or C₁-C₄alkyl; and

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₆alkyl and C₁-C₆alkenyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl;

wherein each of which alkyl, alkenyl and heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, amino, hydroxy, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄alkoxy, C₁-C₆haloalkyl and mono- and di-(C₁-C₄alkyl)amino.

25. A compound or pharmaceutically acceptable form thereof according to claim 24, wherein R₃ is di(C₁-C₄alkyl)amino.

26. A compound or pharmaceutically acceptable form thereof according to claim 24, wherein R₃ is pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl or azepanyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, amino, hydroxy and C₁-C₄alkyl.

27. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₃ is a group of the formula:



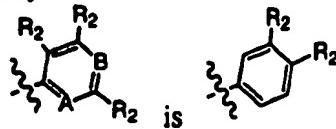
L is a bond or C₁-C₄alkyl; and

R₇ is hydrogen, C₁-C₆alkyl or phenyl(C₀-C₆alkyl), wherein each alkyl and phenylalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, C₁-C₄alkyl, C₁-C₆haloalkyl and C₁-C₆alkoxy.

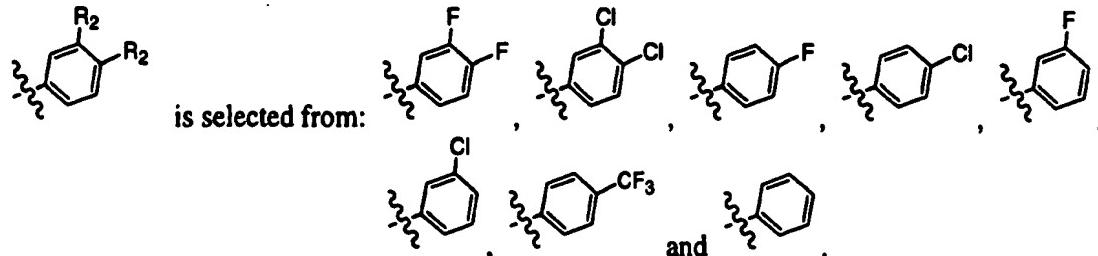
28. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein each R₂ is independently chosen from hydrogen, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

29. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein A and B are CR₂.

30. A compound or pharmaceutically acceptable form thereof according to claim 29, wherein the group represented by:



31. A compound or pharmaceutically acceptable form thereof according to claim 30, wherein:

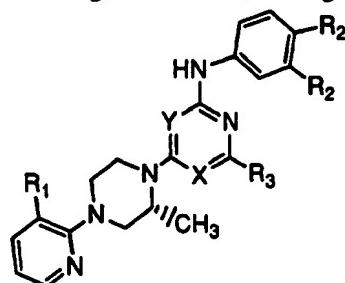


32. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein X is N.

33. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein Y is N.

34. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein Z and X are N.

35. A compound according to claim 18, having the formula:



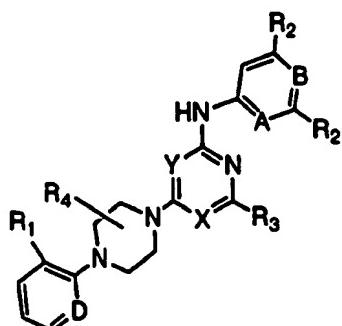
36. A compound according to claim 35, wherein:

R1 is fluoro, chloro, cyano, methyl or trifluoromethyl;
each R2 is independently chosen from hydrogen, halogen, cyano, C1-C4alkyl, C1-C4alkoxy and C1-C4haloalkyl; and

R_3 is mono- or di-(C_1 - C_6 alkyl)amino, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl or benzyloxy, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, amino, hydroxyl, C_1 - C_4 alkyl, cyano, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl and mono- and di-(C_1 - C_6 alkyl)amino.

37. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein the compound exhibits no detectable agonist activity an *in vitro* assay of capsaicin receptor agonism.

38. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A is CH or N;

B is CR₂ or N;

D, X and Y are independently CH or N;

R_1 is halogen, hydroxy, amino, cyano, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkyl ether, C_2 - C_6 alkanoyl, C_3 - C_6 alkanone, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, mono- or di-(C_1 - C_6 alkyl)amino, C_1 - C_6 alkylsulfonyl, mono- or di-(C_1 - C_6 alkyl)sulfonamido, or mono- or di-(C_1 - C_6 alkyl)aminocarbonyl;

Each R_2 is:

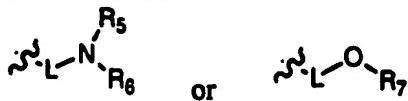
- (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkyl ether, C_2 - C_6 alkanoyl, C_3 - C_6 alkanone, mono- and di-(C_1 - C_6 alkyl)amino, C_1 - C_6 alkylsulfonyl, mono- and di-(C_1 - C_6 alkyl)sulfonamido, and mono- and di-(C_1 - C_6 alkyl)aminocarbonyl; or
- (ii) joined to an adjacent R_2 to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C_1 - C_6 alkyl;

R_3 is selected from:

- (i) hydrogen, hydroxy, halogen and C_1 - C_6 haloalkyl;

(ii) C_1 - C_6 alkyl, phenyl and pyridyl; and

(iii) groups of the formula



wherein

L is a bond or C_1 - C_6 alkyl;

R_5 and R_6 are:

(a) independently chosen from hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_8 alkenyl, C_2 - C_8 alkanoyl, phenyl(C_0 - C_6 alkyl), pyridyl(C_0 - C_6 alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl; and

R_7 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl(C_0 - C_4 alkyl), C_1 - C_8 alkenyl, C_2 - C_8 alkanoyl, phenyl(C_0 - C_6 alkyl), pyridyl(C_0 - C_6 alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_2 - C_6 alkyl ether, C_1 - C_6 alkoxy, C_2 - C_6 alkanoyl, C_1 - C_6 haloalkyl, mono- and di-(C_1 - C_6 alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C_1 - C_4 alkyl, C_1 - C_4 alkoxy and C_1 - C_4 haloalkyl; and

R_4 represents from 0 to 2 methyl substituents.

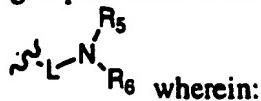
39. A compound or pharmaceutically acceptable form thereof according to claim 38,

wherein D is N.

40. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein R_1 is halogen, amino, cyano, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 alkylsulfonyl and mono- and di-(C_1 - C_6 alkyl)sulfonamido.

41. A compound or pharmaceutically acceptable form thereof according to claim 40, wherein R_1 is fluoro, chloro, cyano, methyl, trifluoromethyl or methylsulfonyl.

42. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein R₃ is a group of the formula:



L is a bond or C₁-C₄alkyl; and

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₆alkyl and C₁-C₆alkenyl; or

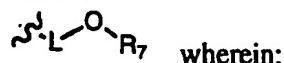
(b) joined to form a 5- to 7-membered heterocycloalkyl;

wherein each of which alkyl, alkenyl and heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, amino, hydroxy, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₄alkyl)amino.

43. A compound or pharmaceutically acceptable form thereof according to claim 42, wherein R₃ is di(C₁-C₄alkyl)amino.

44. A compound or pharmaceutically acceptable form thereof according to claim 42, wherein R₃ is pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl or azepanyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, amino, hydroxy and C₁-C₄alkyl.

45. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein R₃ is a group of the formula:



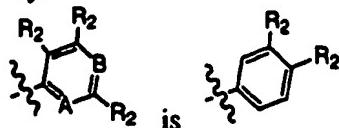
L is a bond or C₁-C₄alkyl; and

R₇ is hydrogen, C₁-C₆alkyl or phenyl(C₀-C₆alkyl), wherein each alkyl and phenylalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, C₁-C₄alkyl, C₁-C₆haloalkyl and C₁-C₆alkoxy.

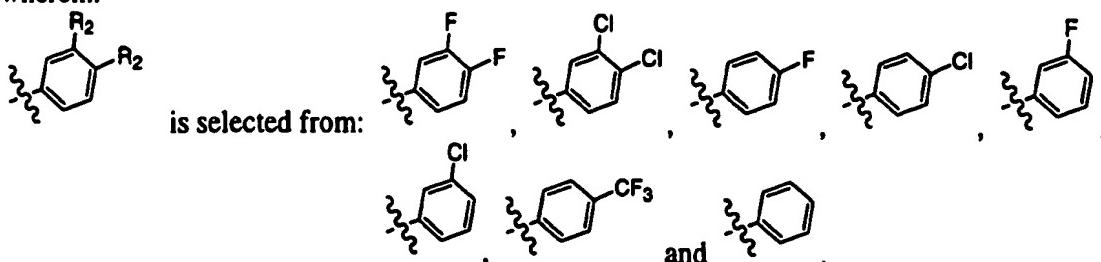
46. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein each R₂ is independently chosen from hydrogen, amino, cyano, halogen, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

47. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein A and B are CR₂.

48. A compound or pharmaceutically acceptable form thereof according to claim 47, wherein the group represented by:



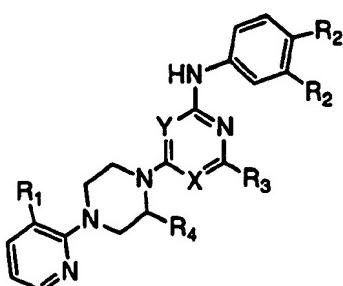
49. A compound or pharmaceutically acceptable form thereof according to claim 48, wherein:



50. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein X is N.

51. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein Y is N.

52. A compound or pharmaceutically acceptable form thereof according to claim 38, having the formula:



wherein R₄ is hydrogen or methyl.

53. A compound or pharmaceutically acceptable form thereof according to claim 52, wherein:

R₁ is fluoro, chloro, cyano, methyl or trifluoromethyl;

each R₂ is independently chosen from hydrogen, halogen, cyano, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₃ is mono- or di-(C₁-C₆alkyl)amino, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl or benzyloxy, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, amino, hydroxyl, C₁-C₄alkyl, cyano, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₆alkyl)amino.

54. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein the compound exhibits no detectable agonist activity an *in vitro* assay of capsaicin receptor agonism.

55. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38, wherein the compound has an IC₅₀ value of 1 micromolar or less in a capsaicin receptor calcium mobilization assay.

56. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38, wherein the compound has an IC₅₀ value of 100 nanomolar or less in a capsaicin receptor calcium mobilization assay.

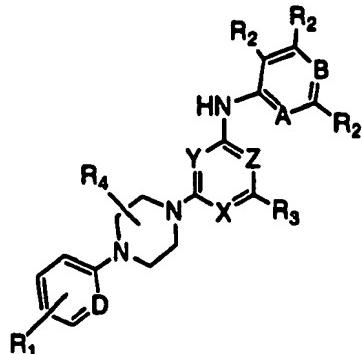
57. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38, wherein the compound has an IC₅₀ value of 10 nanomolar or less in a capsaicin receptor calcium mobilization assay.

58. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38, wherein the compound has an IC₅₀ value of 1 nanomolar or less in a capsaicin receptor calcium mobilization assay.

59. A pharmaceutical composition, comprising at least one compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38 in combination with a physiologically acceptable carrier or excipient.

60. A pharmaceutical composition according to claim 59 wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

61. A method for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell expressing a capsaicin receptor with at least one compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

(i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or

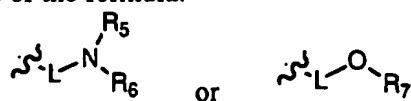
(ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, phenyl and pyridyl; and

(iii) groups of the formula:



wherein

L is a bond or C₁-C₆alkyl;

R_5 and R_6 are:

- (a) independently chosen from hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_8 alkenyl, C_2 - C_8 alkanoyl, phenyl(C_0 - C_6 alkyl), pyridyl(C_0 - C_6 alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or
- (b) joined to form a 5- to 7-membered heterocycloalkyl; and

R_7 is C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl(C_0 - C_4 alkyl), C_1 - C_8 alkenyl, C_2 - C_8 alkanoyl, phenyl(C_0 - C_6 alkyl), pyridyl(C_0 - C_6 alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_2 - C_6 alkyl ether, C_1 - C_6 alkoxy, C_2 - C_6 alkanoyl, C_1 - C_6 haloalkyl, mono- and di-(C_1 - C_6 alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C_1 - C_4 alkyl, C_1 - C_4 alkoxy and C_1 - C_4 haloalkyl; and

R_4 represents from 0 to 2 methyl substituents;

and thereby reducing calcium conductance of the capsaicin receptor.

62. A method according to claim 61, wherein the cell is a neuronal cell that is contacted *in vivo* in an animal.

63. A method according to claim 62 wherein during contact the compound is present within a body fluid of the animal.

64. A method according to claim 63, wherein the compound is present in the blood of the animal at a concentration of 100 nanomolar or less.

65. A method according to claim 62, wherein the animal is a human.

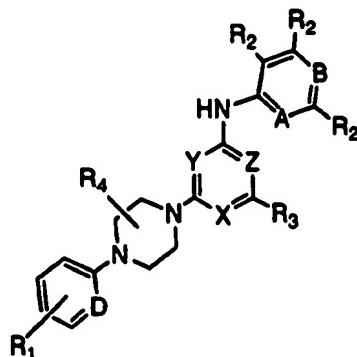
66. A method according to claim 62, wherein the compound is administered orally.

67. A method according to claim 62, wherein the compound is a compound according to claim 1.

68. A method according to claim 62, wherein the compound is a compound according to claim 18.

69. A method according to claim 62, wherein the compound is a compound according to claim 38.

70. A method for inhibiting binding of vanilloid ligand to a capsaicin receptor *in vitro*, the method comprising contacting capsaicin receptor with at least one compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

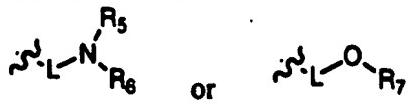
(i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or

(ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl;

R₃ is selected from:

- (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
- (ii) C₁-C₆alkyl, phenyl and pyridyl; and

(iii) groups of the formula:



wherein

L is a bond or C₁-C₆alkyl;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 methyl substituents;

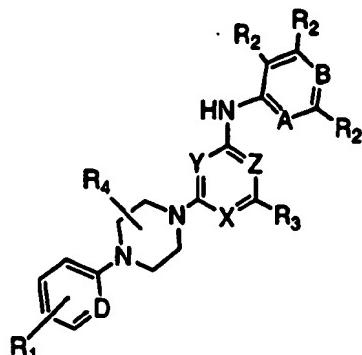
under conditions and in an amount sufficient to detectably inhibit vanilloid ligand binding to capsaicin receptor.

71. A method according to claim 70, wherein the compound is a compound according to claim 1.

72. A method according to claim 70, wherein the compound is a compound according to claim 18.

73. A method according to claim 70, wherein the compound is a compound according to claim 38.

74. A method for inhibiting binding of vanilloid ligand to a capsaicin receptor in a patient, the method comprising contacting cells expressing capsaicin receptor with at least one compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

(i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or

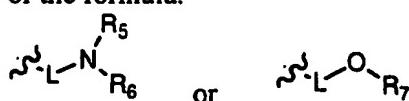
(ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, phenyl and pyridyl; and

(iii) groups of the formula:



wherein

L is a bond or C₁-C₆alkyl;

R₅ and R₆ are:

- (a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or
- (b) joined to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 methyl substituents;

in an amount sufficient to detectably inhibit vanilloid ligand binding to cells expressing a cloned capsaicin receptor *in vitro*, and thereby inhibiting binding of vanilloid ligand to the capsaicin receptor in the patient.

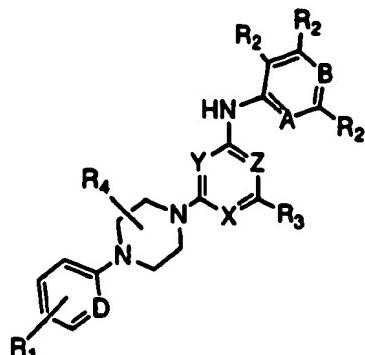
75. A method according to claim 74, wherein the compound or pharmaceutically acceptable form thereof is present in the blood of the patient at a concentration of 100 nanomolar or less.

76. A method according to claim 74, wherein the compound is a compound according to claim 1.

77. A method according to claim 74, wherein the compound is a compound according to claim 18.

78. A method according to claim 74, wherein the compound is a compound according to claim 38.

79. A method for treating a condition responsive to capsaicin receptor modulation in a patient, comprising administering to the patient a capsaicin receptor modulatory amount of a compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

A and **B** are independently CR_2 or **N**;

D is CH or **N**;

X, **Y** and **Z** are independently CR_x or **N**, with the proviso that at least one of **X**, **Y** and **Z** is **N**;

R_x is independently chosen at each occurrence from hydrogen, $\text{C}_1\text{-C}_6$ alkyl and cyano;

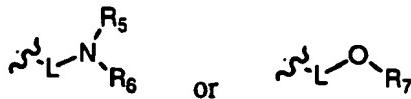
R_1 represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_2\text{-C}_6$ alkyl ether, $\text{C}_2\text{-C}_6$ alkanoyl, $\text{C}_3\text{-C}_6$ alkanone, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, mono- and di-($\text{C}_1\text{-C}_6$ alkyl)amino, $\text{C}_1\text{-C}_6$ alkylsulfonyl, mono- and di-($\text{C}_1\text{-C}_6$ alkyl)sulfonamido, and mono- and di-($\text{C}_1\text{-C}_6$ alkyl)aminocarbonyl;

Each R_2 is:

- (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_2\text{-C}_6$ alkyl ether, $\text{C}_2\text{-C}_6$ alkanoyl, $\text{C}_3\text{-C}_6$ alkanone, mono- and di-($\text{C}_1\text{-C}_6$ alkyl)amino, $\text{C}_1\text{-C}_6$ alkylsulfonyl, mono- and di-($\text{C}_1\text{-C}_6$ alkyl)sulfonamido, and mono- and di-($\text{C}_1\text{-C}_6$ alkyl)aminocarbonyl; or
- (ii) joined to an adjacent R_2 to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and $\text{C}_1\text{-C}_6$ alkyl;

R_3 is selected from:

- (i) hydrogen, hydroxy, halogen and $\text{C}_1\text{-C}_6$ haloalkyl;
- (ii) $\text{C}_1\text{-C}_6$ alkyl, phenyl and pyridyl; and
- (iii) groups of the formula:



wherein

L is a bond or $\text{C}_1\text{-C}_6$ alkyl;

R₅ and **R**₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 methyl substituents;

and thereby alleviating the condition in the patient.

80. A method according to claim 79, wherein the patient is suffering from (i) exposure to capsaicin, (ii) burn or irritation due to exposure to heat, (iii) burns or irritation due to exposure to light, (iv) burn, bronchoconstriction or irritation due to exposure to tear gas, air pollutants or pepper spray, or (v) burn or irritation due to exposure to acid.

81. A method according to claim 79, wherein the compound or pharmaceutically acceptable form thereof is present in the blood of the animal at a concentration of 100 nanomolar or less.

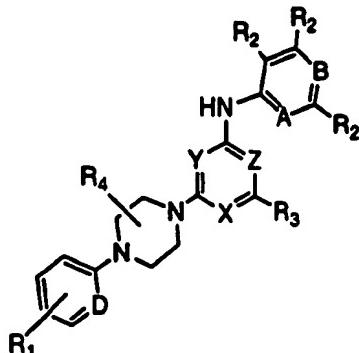
82. A method according to claim 79, wherein the condition is asthma or chronic obstructive pulmonary disease.

83. A method according to claim 79, wherein the compound is a compound according to claim 1.

84. A method according to claim 79, wherein the compound is a compound according to claim 18.

85. A method according to claim 79, wherein the compound is a compound according to claim 38.

86. A method for treating pain in a patient, comprising administering to a patient suffering from pain a capsaicin receptor modulatory amount of at least one compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

(i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or

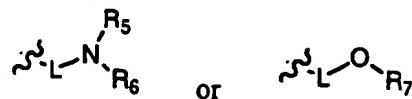
(ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, phenyl and pyridyl; and

(iii) groups of the formula:



wherein

L is a bond or C₁-C₆alkyl;

R₅ and R₆ are:

- (a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or
- (b) joined to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 methyl substituents;

and thereby alleviating pain in the patient.

87. A method according to claim 86, wherein the compound is present in the blood of the animal at a concentration of 100 nanomolar or less.

88. A method according to claim 86, wherein the patient is suffering from neuropathic pain.

89. A method according to claim 86, wherein the pain is associated with a condition selected from: postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, bilateral peripheral neuropathy, causalgia, neuritis, neuronitis, neuralgia, AIDS-related neuropathy, MS-related neuropathy, spinal cord injury-related pain, surgery-related pain, musculoskeletal pain, back pain, headache, migraine, angina, labor, hemorrhoids, dyspepsia, Charcot's pains, intestinal gas, menstruation, cancer, venom exposure, irritable bowel syndrome, inflammatory bowel disease, and/or trauma.

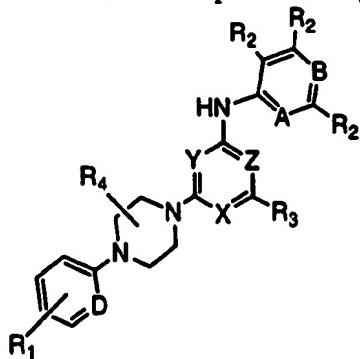
90. A method according to claim 86, wherein the patient is a human.

91. A method according to claim 86, wherein the compound is a compound according to claim 1.

92. A method according to claim 86, wherein the compound is a compound according to claim 18.

93. A method according to claim 86, wherein the compound is a compound according to claim 36.

94. A method for treating itch in a patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

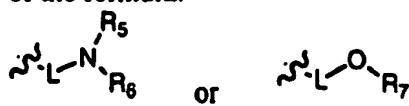
R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

- (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or
- (ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl;

R_3 is selected from:

- (i) hydrogen, hydroxy, halogen and C_1 - C_6 haloalkyl;
- (ii) C_1 - C_6 alkyl, phenyl and pyridyl; and
- (iii) groups of the formula:



wherein

L is a bond or C_1 - C_6 alkyl;

R_5 and R_6 are:

- (a) independently chosen from hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_8 alkenyl, C_2 - C_8 alkanoyl, phenyl(C_0 - C_6 alkyl), pyridyl(C_0 - C_6 alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or
- (b) joined to form a 5- to 7-membered heterocycloalkyl; and

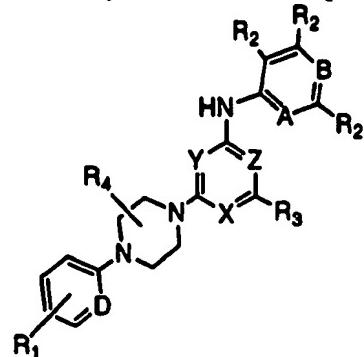
R_7 is C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl(C_0 - C_4 alkyl), C_1 - C_8 alkenyl, C_2 - C_8 alkanoyl, phenyl(C_0 - C_6 alkyl), pyridyl(C_0 - C_6 alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_2 - C_6 alkyl ether, C_1 - C_6 alkoxy, C_2 - C_6 alkanoyl, C_1 - C_6 haloalkyl, mono- and di-(C_1 - C_6 alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C_1 - C_4 alkyl, C_1 - C_4 alkoxy and C_1 - C_4 haloalkyl; and

R_4 represents from 0 to 2 methyl substituents;

and thereby alleviating itch in the patient.

95. A method for treating cough or hiccup in a patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

(i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or

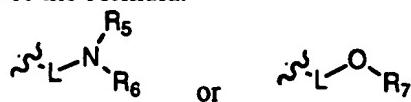
(ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, phenyl and pyridyl; and

(iii) groups of the formula:



wherein

L is a bond or C₁-C₆alkyl;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) joined to form a 5- to 7-membered heterocycloalkyl; and

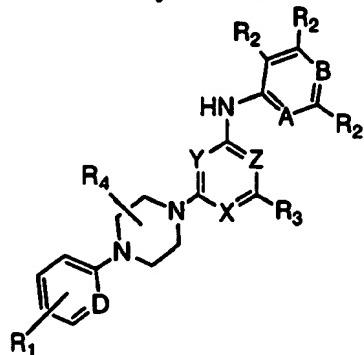
R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 methyl substituents;

and thereby alleviating cough or hiccup in the patient.

96. A method for promoting weight loss in an obese patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, with the proviso that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl and cyano;

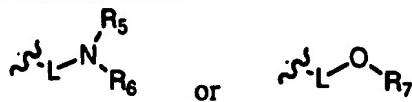
R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

- (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or
- (ii) joined to an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen and C₁-C₆alkyl;

R₃ is selected from:

- (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
- (ii) C₁-C₆alkyl, phenyl and pyridyl; and
- (iii) groups of the formula:



wherein

L is a bond or C₁-C₆alkyl;

R₅ and R₆ are:

- (a) independently chosen from hydrogen, C₁-C₈alkyl, C₃-C₈cycloalkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or
- (b) joined to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, C₃-C₈cycloalkyl(C₀-C₄alkyl), C₁-C₈alkenyl, C₂-C₈alkanoyl, phenyl(C₀-C₆alkyl), pyridyl(C₀-C₆alkyl) or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 methyl substituents;

and thereby promoting weight loss in the patient.

97. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein the compound or pharmaceutically acceptable form thereof is radiolabeled.

98. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein the compound or pharmaceutically acceptable form thereof is radiolabeled.

99. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein the compound or pharmaceutically acceptable form thereof is radiolabeled.

100. A method for determining the presence or absence of capsaicin receptor in a sample, comprising the steps of:

- (a) contacting a sample with a compound or pharmaceutically acceptable form thereof according to claim 1, 18 or 38, under conditions that permit binding of the compound to capsaicin receptor; and
- (b) detecting a level of the compound bound to capsaicin receptor, and therefrom determining the presence or absence of capsaicin receptor in the sample.

101. A method according to claim 100, wherein the compound radiolabeled, and wherein the step of detection comprises the steps of:

- (i) separating unbound compound from bound compound; and
- (ii) detecting the presence or absence of bound compound in the sample.

102. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 59 in a container; and
- (b) instructions for using the composition to treat pain.

103. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 59 in a container; and
- (b) instructions for using the composition to treat cough or hiccup.

104. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 59 in a container; and
- (b) instructions for using the composition to treat obesity.

105. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3,4-Difluorophenyl)(5-methyl-2-morpholin-4-yl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-4-yl)amine.

106. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3,4-Difluoro-phenyl)-{2-(2,6-dimethyl-

morpholin-4-ylmethyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl]-amine.

107. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3,4-Difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine.

108. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3,4-Difluoro-phenyl)-{2-morpholin-4-ylmethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine.

109. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3,4-Difluoro-phenyl)-{4-[4-(3-methanesulfonyl-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine (R).

110. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3,4-Difluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine.

111. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3-Chloro-phenyl)-{4-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine.

112. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine.

113. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine.

114. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine.

115. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (3-Methoxy-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine.

116. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-Chloro-phenyl)-{4-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine.

117. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine.

118. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-Fluoro-phenyl)-[2-morpholin-4-yl-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-4-yl]-amine.

119. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine.

120. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine.

121. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-Fluoro-phenyl)-{6-morpholin-4-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine.

122. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-Methoxy-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine.

123. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-[4-(4-pyridin-2-yl-piperazin-1-yl)-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-amine.

124. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-[4-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-amine (R).

125. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-[4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine.

126. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-[4-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine (R).

127. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-[4-[4-(3-fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine (R).

128. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-(4-chloro-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-amine (R).

129. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-(4-chloro-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl)-amine (R).

130. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-(4-chloro-6-[4-(3-fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl)-amine (R).

131. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is (4-*tert*-Butyl-phenyl)-{6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-pyrimidin-4-yl}-amine (R).

132. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is [4-[2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]- (4-trifluoromethyl-phenyl)-amine (R).

133. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is [4-[2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(4-trifluoromethyl-phenyl)-[1,3,5]triazin-2-yl]- (4-trifluoromethyl-phenyl)-amine (S).

134. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is [4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-{4-trifluoromethyl-phenyl}-amine (R).

135. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is [4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2,4-dimethoxy-phenyl)-[1,3,5]triazin-2-yl]-{4-trifluoromethyl-phenyl}-amine.

136. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is [4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2,4-dimethoxy-phenyl)-[1,3,5]triazin-2-yl]-{4-trifluoromethyl-phenyl}-amine.

137. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is [4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-(2-methyl-pyrrolidin-1-yl)-[1,3,5]triazin-2-yl]-{3-fluoro-phenyl}-amine.

138. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is [4-[4-(3-Fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzylxy)-[1,3,5]triazin-2-yl]-{4-trifluoromethyl-phenyl}-amine (R).

139. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {2-Diethylaminomethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-{3,4-difluoro-phenyl}-amine.

140. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-(2-Chloro-phenyl)-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-{4-trifluoromethyl-phenyl}-amine (S).

141. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-(4-Butyl-phenyl)-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-{4-trifluoromethyl-phenyl}-amine.

142. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-(3,4-Difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-methanol.

143. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4,6-Bis-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl)-(4-trifluoromethyl-phenyl)-amine.

144. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(3,4-difluoro-phenyl)-amine (R).

145. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(3-fluoro-phenyl)-amine.

146. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-methyl-[1,3,5]triazin-2-yl)-(4-trifluoromethyl-phenyl)-amine.

147. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(3-fluoro-phenyl)-amine.

148. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(4-fluoro-phenyl)-amine.

149. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-p-tolyl-amine.

150. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(3,4-difluoro-phenyl)-amine.

151. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-(4-trifluoromethyl-phenyl)-amine.

152. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl)-phenyl-amine.

153. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-piperidin-1-yl-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine.

154. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-piperidin-1-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine.

155. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-pyrrolidin-1-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine.

156. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Azepan-1-yl-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine.

157. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Chloro-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine (S).

158. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Chloro-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-amine (R).

159. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Chloro-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine.

160. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine.

161. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-p-tolyl-amine.

162. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-o-tolyl-amine.

163. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-m-tolyl-amine.

164. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-p-tolyl-amine.

165. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {6-Chloro-2-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-pyrimidin-4-yl}-(4-trifluoromethyl-phenyl)-amine (R).

166. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is {6-Morpholin-4-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-p-tolyl-amine.

167. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 4-{4-(3-chloro-4-fluoro-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-morpholine.

168. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 4-{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-diethylamino-[1,3,5]triazin-2-ylamino}-benzonitrile.

169. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3,4-difluoro-phenyl)-N',N'-diethyl-[1,3,5]triazine-2,4-diamine (R).

170. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-methyl-butyl)-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R).

171. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-

piperazin-1-yl]-N-(3-methyl-butyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

172. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-phenyl-propyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

173. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-trifluoromethyl-benzyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

174. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

175. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (S).

176. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dipropyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

177. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isobutyl-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R).

178. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isobutyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

179. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

180. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-methyl-N-propyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

181. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-propyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

182. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-propyl-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R).

183. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3,4-difluoro-phenyl)-N',N'-diethyl-[1,3,5]triazine-2,4-diamine.

184. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-methyl-N'-propyl-[1,3,5]triazine-2,4-diamine.

185. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N',N'-dimethyl-[1,3,5]triazine-2,4-diamine.

186. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-isopropyl-N'-methyl-[1,3,5]triazine-2,4-diamine.

187. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-propyl-[1,3,5]triazine-2,4-diamine.

188. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine.

189. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3-methoxy-phenyl)-[1,3,5]triazine-2,4-diamine.

190. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(4-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine.

191. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine.

192. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N'-(3-fluoro-phenyl)-N-methyl-[1,3,5]triazine-2,4-diamine.

193. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N'-(3-fluoro-phenyl)-N-isopropyl-[1,3,5]triazine-2,4-diamine.

194. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N-isopropyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine.

195. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine.

196. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-isopropyl-N-methyl-N'-phenyl-[1,3,5]triazine-2,4-diamine.

197. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine.

198. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-(2,5-Dimethoxy-phenyl)-N',N'-diethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine.

199. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine.

200. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine (R).

201. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-[4-(3-methanesulfonyl-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine (R).

202. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-(3-Chloro-phenyl)-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-N',N'-diethyl-[1,3,5]triazine-2,4-diamine.

203. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-(3-Methyl-butyl)-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (S).

204. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-(3-Methyl-butyl)-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine.

205. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N,N-Diallyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

206. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N,N-Dibutyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

207. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N,N-Diethyl-N'-(4-fluoro-phenyl)-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine.

208. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N,N-Dimethyl-6-(4-phenyl-piperazin-1-yl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine.

209. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N,N-Dimethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine.

210. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N,N-Dimethyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine.

211. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N,N-Dimethyl-N'-phenyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine.

212. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Benzyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

213. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Butyl-6-[4-(2-chloro-phenyl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R).

214. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

215. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

216. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R).

217. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-N'-(3-fluoro-phenyl)-N-methyl-[1,3,5]triazine-2,4-diamine.

218. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine.

219. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Isopropyl-N-methyl-N'-phenyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine.

220. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-Methyl-N-propyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine.

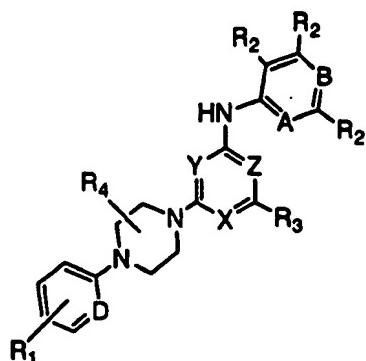
221. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is N-sec-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R).

222. A compound or pharmaceutically acceptable form thereof according to one or more of claims 1, 18 and 38, wherein the compound is Phenyl-{6-piperidin-1-yl}-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine.

ABSTRACT OF THE DISCLOSURE

SUBSTITUTED HETEROCYCLIC DIARYLAMINE ANALOGUES

Substituted heterocyclic diarylamine analogues of Formula I are provided:



, wherein X, Y, Z, A, B and D are independently N or optionally substituted C, and other variables are as described in the specification. Such compounds are ligands that may be used to modulate specific receptor activity *in vivo* or *in vitro*, and are particularly useful in the treatment of conditions associated with pathological receptor activation in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for using them to treat such disorders are provided, as are methods for using such ligands for receptor localization studies.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney's Docket No. N03.2202P

**Applicant or
Patentee:** Rajagopal Bakthavatchalam, et al.

**Serial or
Patent No.** Not Yet Assigned **Filed:** Herewith

Title: Substituted Heterocyclic Diarylamine Analogues

**VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS
(37 C.F.R. § 1.9(f) AND § 1.27(c)) - SMALL BUSINESS CONCERN**

I hereby declare that I am an official of the small business concern empowered to act on behalf of the concern identified below:

US Express Mailing No. ER139646075US

NAME OF SMALL BUSINESS CONCERN

NEUROGEN CORPORATION

ADDRESS OF SMALL BUSINESS CONCERN

35 NORTHEAST INDUSTRIAL ROAD
BRANFORD, CT 06405

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 C.F.R. § 121, and referenced in 37 C.F.R. § 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled Substituted Heterocyclic Diarylamine Analogues by inventors Rajagopal Bakthavatchalam, Charles A. Blum, Stephane DeLombaert, Alan Hutchison, Robert Ohliger, John M. Peterson, Taeyoung Yoon and Xiaozhang Zheng.

described in



the specification filed herewith.



Application Serial No. _____, filed _____.



Patent No. _____, issued _____.

Patent Department
NEUROGEN CORPORATION
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

If the rights held by the above identified small business concern are not exclusive, each individual concern or organization having rights in the invention must file verified statements averring to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR § 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR § 1.9(d), or a nonprofit organization under 37 CFR § 1.9(e).

Each person, concern or organization having any rights to the invention is listed below:

- No such person, concern or organization exists.
 Each such person, concern or organization is listed below.

FULL NAME _____ **ADDRESS**

- Individual Small Business Concern Nonprofit Organization

Separate verified statements are required from each named person, concern or organization having rights in the invention averring to their status as small entities. (37 CFR § 1.27).

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. § 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing therein, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Seth Fidel

TITLE IN ORGANIZATION: Assistant Secretary to the Corporation

ADDRESS OF PERSON SIGNING: 35 Northeast Industrial Road
Branford, CT06405

Signature: John Smith 38949

Date: 10 July 2003

**Patent Department
NEUROGEN CORPORATION
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201**

Customer I.D. 29441

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. N03.2202P

In re the application of: Rajagopal Bakthavatchalam, et al.

For: Substituted Heterocyclic Diarylamine Analogues

Mail Stop Provisional Patent Application

Commissioner For Patents

P.O. Box 1450

Alexandria, VA 22313-1450

16447 U.S. PRO
60/406133
07/09/03

COVER SHEET FOR FILING PROVISIONAL PATENT APPLICATION

Dear Sir:

The accompanying application, entitled Substituted Heterocyclic Diarylamine Analogues, is a provisional patent application under 37 C.F.R. § 1.51 (a)(2) and § 1.53 (b)(2).

US Express Mailing No. ER139646075US

1. The names and addresses of the inventors of this application are as follows:

	Last Name	First Name	Middle Initial	Residence
1.	Bakthavatchalam	Rajagopal		67 Hickory Lane Madison, CT 06443
2.	Blum	Charles	A.	785 W. Pond Meadow Rd. Westbrook, CT 06498
3.	DeLombaert	Stéphane		37 Concord Drive Madison, CT 06443
4.	Hutchison	Alan		28 Kimberly Lane Madison, CT 06443
5.	Ohliger	Robert		2115 Durham Road Madison, CT 06443
6.	Peterson	John	M.	119 Maple Avenue Durham, CT 06422
7.	Yoon	Taeyoung		6 Finch Lane Guilford, CT 06437
8.	Zheng	Xiaozhang		10 Roby Court Branford, CT 06405

2. This invention was made by an agency of the United States Government or under contract with an agency of the United States Government. The name of the U.S. Government agency and the Government contract number are:

Agency: _____

Contract No.: _____

Customer I.D. 29441

Attorney Docket: N03.2202P

3. The following documents are enclosed:

- 123 pages of Specification
 1 page of abstract
 _____ pages of drawings

4. A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.
5. An Assignment of the invention to _____ is enclosed. A check in the amount of \$40.00 for recording this assignment and a recordation form cover sheet (Form PTO 1595) are also enclosed.
6. The fee for filing this provisional application, as set forth in 37 CFR 1.16(k), is \$80.00.
- a. A check for this filing is enclosed.
 - b. Charge the filing fee to Deposit Account No. 501116.
 - c. The filing fee is not being paid at this time.
7. Please charge any fee deficiencies associated with this filing to Deposit Account No. 501116.
A duplicate copy of this sheet is enclosed.

Please address all future communications to:

Patent Department
Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405

and direct telephone calls to: Seth A. Fidel or Ann Kadlecuk.

Respectfully submitted,

7/10/2003

Date


Ann Kadlecuk
Registration No. 39,244

Seth A. Fidel
Registration No. 38,449

Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

Customer I.D. 29441

[x] Attorney Docket No. : N03.2202P

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rajagopal Bakthavatchalam, et al.

Serial No. : Not Yet Assigned

Filed : Herewith

For : Substituted Heterocyclic Diarylamine Analogues

Mail Stop Provisional Patent Application

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

EXPRESS MAIL INFORMATION

Attached hereto are the following papers which are to be sent by Express Mail Post Office To Addressee Service to: Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on July 10, 2003:

1. Provisional Application for Patent Cover Sheet (2 sheets, 2 copies)
2. Specification for Patent Application: "Substituted Heterocyclic Diarylamine Analogues" (123 pages)
3. Abstract for patent application (1 page)
4. Check for Provisional Application Filing Fee (1 check, \$80.00)
5. Verified Statement Claiming Small Entity Status (2 pages)
6. Return Postcard (1 card)

Express Mail Mailing Label No. ER139646075US

Respectfully submitted:

Ann T. Kadlecak

Reg. No. 39,244

Neurogen Corp.

35 NE Industrial Rd.

Branford, CT 06405

7/10/2003
Date

K
Signed

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/022326

International filing date: 09 July 2004 (09.07.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/486,133
Filing date: 10 July 2003 (10.07.2003)

Date of receipt at the International Bureau: 08 October 2004 (08.10.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

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